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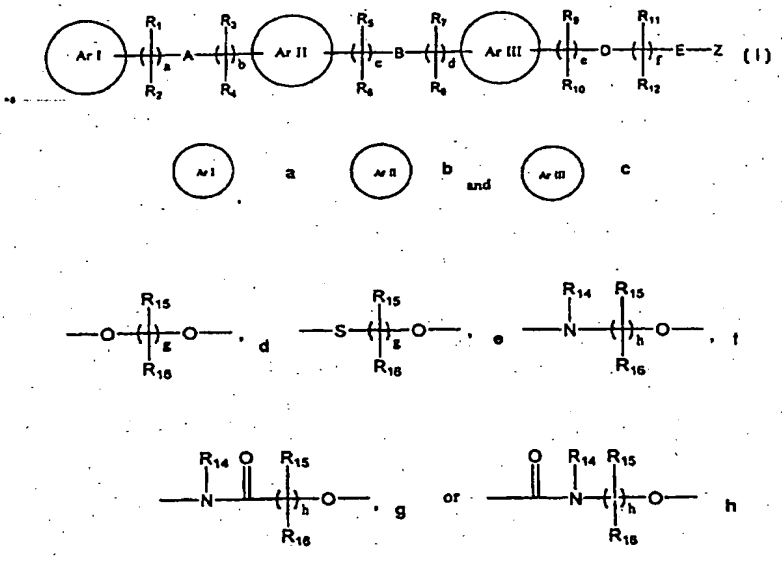
(54) Title: TRI-ARYL ACID DERIVATIVES AS PPAR RECEPTOR LIGANDS

(57) Abstract

This invention is directed to triaryl acid derivatives of formula (I) and their pharmaceutical compositions as PPAR ligand receptor binders. The PPAR ligand receptor binders of this invention are useful as agonists or antagonists of the PPAR receptor. In formula (I), (a), (b), and (c) are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkemyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl; A is –O–, –S–, –SO–, $-SO_2-$, $-NR_{13}-$, –C(O)–, $-N(R_{14})C(O)-$, $-C(O)N(R_{15})-$, $-N(R_{14})C(O)N(R_{15})-$, $-C(R_{14})=N-$, (d), (e), (f) a chemical bond, (g) or (h); B is –O–, –S–, –SO–, $-SO_2-$, $-NR_{17}-$, a chemical bond, ethynylene, –C(O)–, $-N(R_{18})C(O)-$, or $-C(O)NR_{18}-$; D is –O–, –S–, $-NR_{19}-$, a chemical bond, ethynylene, –C(O)–, $-N(R_{20})C(O)-$, or $-C(O)N(R_{20})-$; E is a chemical bond or an ethylene group; Z is $R_{21}O_2C-$, $R_{21}OC-$, cyclo-imide, –CN, $R_{21}O_2SHNCO-$, $R_{21}O_2SHN-$, $(R_{21})_2NCO-$, $R_{21}O$–2,4–thiazolidinedionyl, or tetrazolyl.



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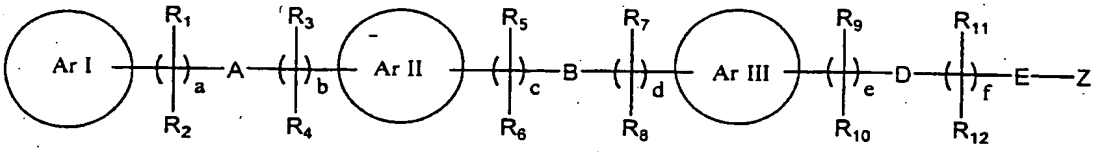
What is claimed is:

1. A compound of formula I



(I)

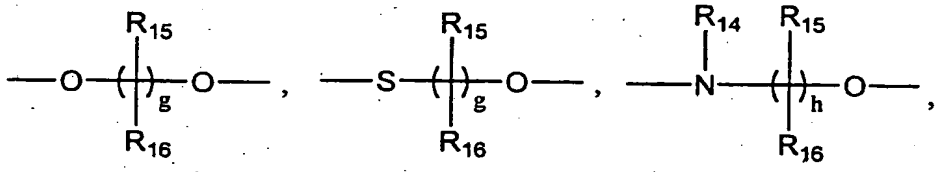
wherein:

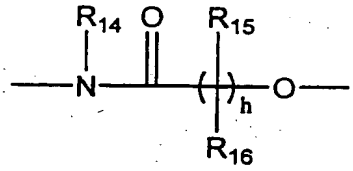
, 

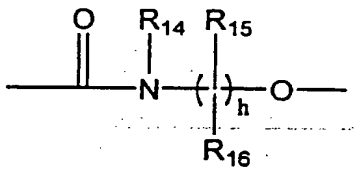
, and 

are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

A is -O-, -S-, -SO-, -SO_2-, -NR_{13}-, -C(O)-, -$N(R_{14})C(O)$-, -$C(O)N(R_{15})$-, -$N(R_{14})C(O)N(R_{15})$-, -$C(R_{14})$=N-, a chemical bond,





, or 

;

B is –O-, -S-, -SO-, -SO_2-, -NR_{17}-, a chemical bond, ethynylene, -C(O)-, -$N(R_{18})C(O)$-, or –$C(O)NR_{18}$-;

D is –O-, -S-, -NR_{19}-, a chemical bond, ethynylene, -$N(R_{20})C(O)$-, -C(O)-, or –$C(O)N(R_{20})$-;

E is a chemical bond or an ethylene group;

a is 0-4;

b is 0-4;

c is 0-4;

d is 0-5;

e is 0-4;

f is 0-6;

g is 1-4;

h is 1-4;

R_1, R_3, R_5, R_7, R_9, and R_{11}, are independently hydrogen, halogen, alkyl, carboxyl, alkoxycarbonyl or aralkyl;

R_2, R_4, R_6, R_8, R_{10} and R_{12}, are independently $-(CH_2)_q-X$;

q is 0-3;

X is hydrogen, halogen, alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, carboxyl, alkoxycarbonyl, tetrazolyl, acyl, acylHNSO$_2$-, -SR$_{23}$, Y^1Y^2N- or Y^3Y^4NCO-;

Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or one of Y^1 and Y^2 is hydrogen or alkyl and the other of Y^1 and Y^2 is acyl or aroyl;

Y^3 and Y^4 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl;

Z is $R_{21}O_2C$-, $R_{21}OC$-, cyclo-imide, -CN, $R_{21}O_2SHNCO$-, $R_{21}O_2SHN$-, $(R_{21})_2NCO$-, $R_{21}O$- 2,4-thiazolidinedionyl, or tetrazolyl; and

R_{19} and R_{21} are independently hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

R_{13}, R_{17}, R_{19} and R_{23} are independently $R_{22}OC$-, $R_{22}NHOC$-, hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl;

R_{14}, R_{15}, R_{16}, R_{18} and R_{20} are independently hydrogen, alkyl, aralkyl, carbonyl, or alkoxycarbonyl;

or R_{14}, and R_{15} taken together with the carbon and nitrogen atoms through which they are linked form a 5 or 6-membered azaheterocyclyl group; or

when a is 2-4, then vicinal R_1 radicals taken together with the carbon atoms to which the R_1 radicals are linked form an ethylene group;or

when b is 2-4, then vicinal R_3 radicals taken together with the carbon atoms to which the R_3 radicals are linked form an ethylene group; or

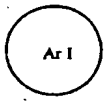
when c is 2-4, then vicinal R_5 radicals taken together with the carbon atoms to which the R_5 radicals are linked form an ethylene group; or

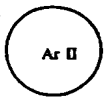
when d is 2-5, then vicinal R_7 radicals taken together with the carbon atoms to which the R_7 radicals are linked form an ethylene group; or

when e is 2-4, then vicinal R_9 radicals taken together with the carbon atoms to which the R_9 radicals are linked form an ethylene group; or

when f is 2-6, then vicinal R_{11} radicals taken together with the carbon atoms to which the R_{11} radicals are linked form an ethylene group; and

R_{22} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl; or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

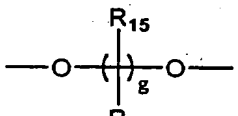
2. A compound according to claim 1 wherein 

is optionally substituted aryl, optionally substituted azaheteroaryl, or optionally substituted fused arylheterocyclenyl; 

is optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted fused arylheterocyclenyl; and 

is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted fused arylheterocyclalkyl or optionally substituted fused arylheterocyclenyl.

3. A compound according to claim 1 wherein a = 1 or 2; R_1 and R_2 is hydrogen; A is a chemical bond; and b = 0.

4. A compound according to claim 1 wherein a = 0; A is 

; R_{15} and R_{16} are hydrogen; g is 1, 2, or 3; and b = 0.

5. A compound according to claim 1 wherein a = 0; A is $-NR_{13}-$, b = 1, R_3 and R_4 are hydrogen.

6. A compound according to claim 1 wherein a = 2; vicinal R_1 radicals taken together with the carbon atoms to which the R_1 radicals are linked form an ethylene group; R_2 is hydrogen; A is a chemical bond; and b=0.

7. A compound according to claim 1 wherein a = 1, 2 or 3; R_1 and R_2 are hydrogen; A is -O-; and b = 0.

8. A compound according to claim 1 wherein a = 1; R_1, R_2, R_3 and R_4 are hydrogen; A is -O-; and b = 1.

9. A compound according to claim 1 wherein c = 1 or 2; R_5 and R_6 are hydrogen or alkyl; B is a chemical bond; and d = 0.

10. A compound according to claim 1 wherein c = 2; vicinal R_5 radicals taken together with the carbon atoms to which the R_5 radicals are linked form an ethylene group; R_6 is hydrogen; B is a chemical bond; and d=0.

11. A compound according to claim 1 wherein c = 0 or 1; R_5 and R_6 are hydrogen; B is –O-; and d = 0 or 1.

12. A compound according to claim 1 wherein c = 0; B is –C(O)- or $-S(O)_2-$; d = 1 and R_7 and R_8 are independently hydrogen or alkyl.

13. A compound according to claim 1 wherein e = 0; f = 0; D and E is a chemical bond; Z is $R_{21}O_2SHNCO-$, and R_{21} is phenyl.

14. A compound according to claim 1 wherein e = 0; f = 0 or 1; D and E is a chemical bond; Z is tetrazolyl, NH_2CO- or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

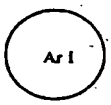
15. A compound according to claim 1 wherein e = 0; f = 0 or 1; D is –O- or a chemical bond; E is a chemical bond; and Z is tetrazolyl, NH_2CO- or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

16. A compound according to claim 1 wherein e = 0; f = 1; D is –O- or a chemical bond; E is a chemical bond; R_{11} and R_{12} are hydrogen or alkyl; and Z is tetrazolyl, NH_2CO- or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

17. A compound according to claim 1 wherein e = 2, then vicinal R_9 radicals taken together with the carbon atoms to which the R_9 radicals are linked form an ethylene group; f = 0; D and E is a chemical bond; and Z is $-CO_2R_{21}$; and R_{21} is hydrogen.

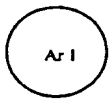
18. A compound according to claim 1 wherein e = 0; f = 3; D is -O-; E is a chemical bond; R_{11} and R_{12} are hydrogen or alkyl, or at least one of R_{11} is carboxyl or alkoxycarbonyl; Z is tetrazolyl, or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

19. A compound according to claim 1 wherein e = 0; f = 1, 2, or 3; D is -C(O)-; E is a chemical bond; R_{11} and R_{12} are hydrogen or alkyl; Z is tetrazolyl or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

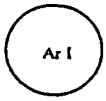
20. A compound according to claim 1 wherein 

is an optionally substituted quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, *N*-alkyl-quinolin-4-onyl, quinazolin-4-onyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, indolinyl oxazolyl, thiazolyl, oxadiazolyl isoxazolyl, imidazolyl, pyrazol-yl, thiadiazolyl, triazolyl, pyridyl pyrimidinyl, pyrazinyl, pyridazinyl, phenyl, or napthalenyl group, wherein the substituent is a

ring system substituent as defined herein, more preferably a substituent selected from the group consisting of phenyl, substituted-phenyl, thienyl, substituted thienyl, cycloalkyl, lower alkyl, branched alkyl, fluoro, chloro, alkoxy, aralkyloxy, trifluoromethyl and trifluoromethyloxy.

21. A compound according to claim 1 wherein 

is unsubstituted quinolin-2-yl, 3-substituted quinolin-2-yl, 4-substituted quinolin-2-yl, 6-substituted quinolin-2-yl or 7 substituted quinolin-2-yl; an unsubstituted quinozalin-2-yl, 3-substituted quinozalin-2-yl, 6-substituted quinozalin-2-yl or 3,6-disubstituted quinozalin-2-yl; unsubstituted quinazolin-2-yl, 4-substituted quinazolin-2-yl or 6-substituted quinazolin-2-yl; unsubstituted isoquinolin-3-yl, 6-substituted isoquinolin-3-yl or 7-substituted isoquinolin-3-yl; 3-substituted-quinazolin-4-on-2-yl; *N*-substituted quinolin-4-on-2-yl; 2-substituted-oxazol-4-yl or 2,5 disubstituted-oxazol-4-yl; 4-substituted oxazol-2-yl or 4,5-disubstituted-oxazol-2-yl; 2-substituted thiazol-4-yl or 2,5-disubstituted thiazol-4-yl; 4-substituted thiazol-2-yl or 4,5-disubstituted-thiazol-2-yl; 5-substituted-[1,2,4]oxadiazol-3-yl; 3-substituted-[1,2,4] oxadiazol-5-yl; 5-substituted-imidazol-2-yl or 3,5-disubstituted-imidazol-2-yl; 2-substituted-imidazol-5-yl or 2,3-disubstituted-imidazol-5-yl; 3-substituted-isoxazol-5-yl; 5-substituted-isoxazol-3-yl; 5-substituted-[1,2,4] thiadiazol-3-yl; 3-substituted-[1,2,4]-thiadiazol-5-yl; 2-substituted-[1,3,4]-thiadiazol-5-yl; 2-substituted-[1,3,4]-oxadiazol-5-yl; 1-substituted-pyrazol-3-yl; 3-substituted-pyrazol-5-yl; 3-substituted-[1,2,4]-triazol-5-yl; 1-substituted-[1,2,4]-triazol-3-yl; 3-substituted pyridin-2-yl, 5-substituted pyridin-2-yl, 6-substituted pyridin-2-yl or 3,5-disubstituted pyridin-2-yl; 3-substituted pyrazin-2-yl, 5-substituted pyrazin-2-yl, 6-substituted pyrazin-2-yl or 3,5 disubstituted-pyrazin-2-yl; 5-substituted pyrimidin-2-yl or 6-substituted-pyrimidin-2-yl; 6-substituted-pyridazin-3-yl or 4,6-disubstituted-pyridazin-3-yl; unsubstituted napthalen-2-yl, 3-substituted napthalen-2-yl, 4-substituted napthalen-2-yl, 6-substituted napthalen-2-yl or 7 substituted napthalen-2-yl; 2-substituted phenyl, 4-substituted phenyl or 2,4-disubstituted phenyl; unsubstituted -benzothiazol-2-yl or 5-substituted-benzothiazol-2-yl; unsubstituted benzoxazol-2yl or 5-substituted-benzoxazol-2yl; unsubstituted -benzimidazol-2-yl or 5-substituted-benzimidazol-2-yl; unsubstituted -thiophen-2yl, 3-substituted -thiophen-2yl, 6-substituted -thiophen-2yl or 3,6-disubstituted-thiophen-2yl; unsubstituted -benzofuran-2-y, 3-substituted-benzofuran-2-yl, 6-substituted-benzofuran-2-yl or 3,6-disubstituted-benzofuran-2-yl; 3-substituted-benzofuran-6-yl or 3,7-disubstituted-benzofuran-6-yl, wherein the substituent is a ring system substituent.

22 A compound according to claim 21 wherein  is substituted by a substituent selected from the group consisting of phenyl, substituted-phenyl, thienyl, substituted thienyl,. cycloalkyl, lower alkyl, branched alkyl, fluoro, chloro, alkoxy, aralkyloxy, trifluoromethyl and trifluoromethyloxy.

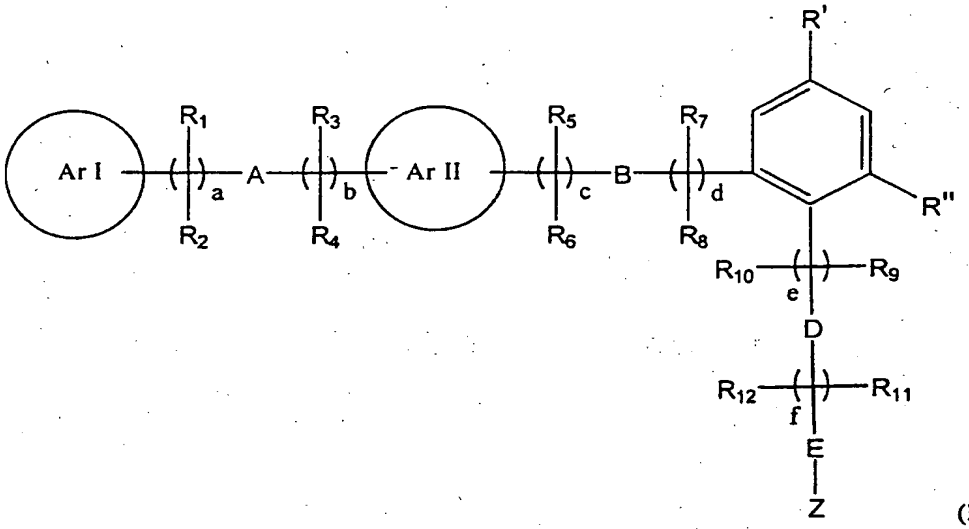
23. A compound according to claim 1 wherein R_1 and R_2 are hydrogen; a = 1; A is –O-; and b = 0.

24. A compound according to claim 1 wherein R_1 and R_2 are hydrogen; a = 2; A is –O-; and b = 0.

25. A compound according to claim 1 wherein a = 0; A is –O- or $-NR_{13}-$; R_{13} is hydrogen or alkyl; R_3 and R_4 are both independently hydrogen; and b = 1.

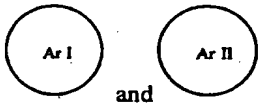
26. A compound according to claim 1 wherein a = 0; A is –O- or $-NR_{13}-$; R_{13} is hydrogen or alkyl; R_3 and R_4 are both independently hydrogen; b = 1; and  is 3-substituted quinolin-2-yl, 4-substituted quinolin-2-yl, 6-substituted quinolin-2-yl, 7 substituted quinolin-2-yl, unsubstituted quinoxalin-2-yl, 3-substituted quinoxalin-2-yl, 6-substituted quinoxalin-2-yl, 3,6-disubstituted quinoxalin-2-yl, unsubstituted quinazolin-2-yl, 4-substituted quinazolin-2-yl, 6-substituted quinazolin-2-yl, unsubstituted isoquinolin-3-yl, 6-substituted isoquinolin-3-yl, 7-substituted isoquinolin-3-yl, 4-substituted oxazol-2-yl, 4,5-disubstituted-oxazol-2-yl, 4-substituted-thiazol-2-yl, 4,5-disubstituted-thiazol-2-yl, 5-substituted -imidazol-2-yl, 3,5-disubstituted-imidazol-2-yl, 1-substituted-pyrazol-3-yl, 3-substituted-pyrazol-5-yl, 3-substituted pyridin-2-yl, 5-substituted pyridin-2-yl, 6-substituted pyridin-2-yl or 3,5-disubstituted pyridin-2-yl, 3-substituted pyrazin-2-yl, 5-substituted pyrazin-2-yl, 6-substituted pyrazin-2-yl, 3,5 disubstituted-pyrazin-2-yl, 5-substituted pyrimidin-2-yl, 6-substituted-pyrimidin-2-yl, 6-substituted-pyridazin-3-yl, 4,6-disubstituted-pyridazin-3-yl, unsubstituted-benzothiazol-2-yl, 5-substituted-benzothiazol-2-yl, unsubstituted-benzoxazol-2-yl, 5-substituted-benzoxazol-2-yl, unsubstituted benzimidazol-2-yl, 5-substituted-benzimidazol-2-yl, 3-substituted-benzofuran-6-yl or 3,7-disubstituted-benzofuran-6-yl.

27. A compound of formula (Ia)



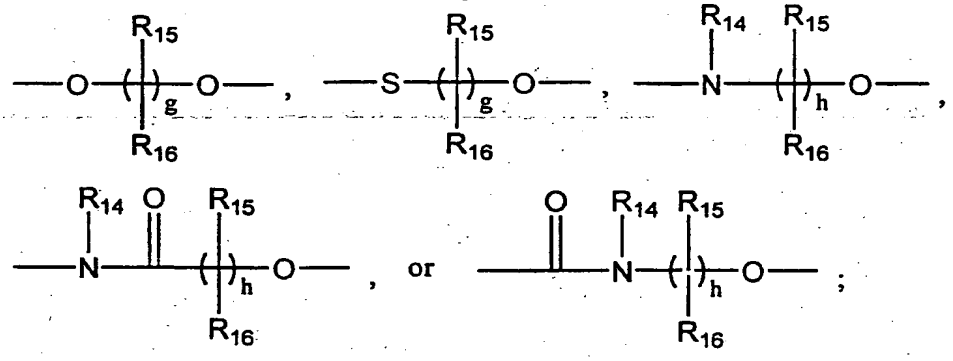
(Ia)

wherein:



and are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

A is -O-, -S-, -SO-, $-SO_2$-, $-NR_{13}$-, -C(O)-, $-N(R_{14})C(O)$-, $-C(O)N(R_{15})$-, $-N(R_{14})C(O)N(R_{15})$-, $-C(R_{14})=N$-, a chemical bond,



B is –O-, -S-, -SO-, $-SO_2$-, $-NR_{17}$-, a chemical bond, ethynylene, -C(O)-, $-N(R_{18})C(O)$-, or $-C(O)NR_{18}$-;

D is –O-, -S-, $-NR_{19}$-, a chemical bond, ethynylene, $-N(R_{20})C(O)$-, -C(O)-, or $-C(O)N(R_{20})$-;

E is a chemical bond or an ethylene group;

a is 0-4;

b is 0-4;

c is 0-4;

d is 0-5;

e is 0-4;

f is 0-6;

g is 1-4;

h is 1-4;

R_1, R_3, R_5, R_7, R_9, and R_{11}, are independently hydrogen, halogen, alkyl, carboxyl, alkoxycarbonyl or aralkyl;

R_2, R_4, R_6, R_8, R_{10} and R_{12}, are independently $-(CH_2)_q-X$;

q is 0-3;

X is hydrogen, halogen, alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, carboxyl, alkoxycarbonyl, tetrazolyl, acyl, acylHNSO$_2$-, -SR$_{23}$, Y^1Y^2N- or Y^3Y^4NCO-;

Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or one of Y^1 and Y^2 is hydrogen or alkyl and the other of Y^1 and Y^2 is acyl or aroyl;

Y^3 and Y^4 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl;

Z is $R_{21}O_2C$-, $R_{21}OC$-, cyclo-imide, -CN, $R_{21}O_2SHNCO$-, $R_{21}O_2SHN$-, $(R_{21})_2NCO$-, $R_{21}O$- 2,4-thiazolidinedionyl, or tetrazolyl;

R' and R" are ring system substituents;

R_{19} and R_{21} are independently hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

R_{13}, R_{17}, R_{19} and R_{23} are independently $R_{22}OC$-, $R_{22}NHOC$-, hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl;

R_{14}, R_{15}, R_{16}, R_{18} and R_{20} are independently hydrogen, alkyl, aralkyl, carbonyl, or alkoxycarbonyl;

or R_{14}, and R_{15} taken together with the carbon and nitrogen atoms through which they are linked form a 5 or 6-membered azaheterocyclyl group; or

when a is 2-4, then vicinal R_1 radicals taken together with the carbon atoms to which the R_1 radicals are linked form an ethylene group;or

when b is 2-4, then vicinal R_3 radicals taken together with the carbon atoms to which the R_3 radicals are linked form an ethylene group; or

when c is 2-4, then vicinal R_5 radicals taken together with the carbon atoms to which the R_5 radicals are linked form an ethylene group; or

when d is 2-5, then vicinal R_7 radicals taken together with the carbon atoms to which the R_7 radicals are linked form an ethylene group; or

when e is 2-4, then vicinal R_9 radicals taken together with the carbon atoms to which the R_9 radicals are linked form an ethylene group; or

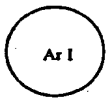
when f is 2-6, then vicinal R_{11} radicals taken together with the carbon atoms to which the R_{11} radicals are linked form an ethylene group; and

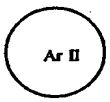
R_{22} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl; or

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

28. A compound according to claim 27

wherein



and


are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

c+d = 1 or 2;

B is –O-;

R_5, R_6, R_7, R_8 are independently hydrogen;

e = 0;

f = 0;

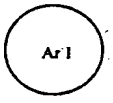
D and E are a chemical bond;

Z is $R_{21}O_2C$-, $R_{21}OC$-, cyclo-imide, -CN, $R_{21}O_2SHNCO$-, $R_{21}O_2SHN$-, $(R_{21})_2NCO$-, $R_{21}O$- 2,4-thiazolidinedionyl, or tetrazolyl;

R' is lower alkyl, halo, alkoxy, aryloxy or aralkyl; and

R" is lower alkyl or halo.

29. A compound according to claim 27 wherein



and


are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

c+d = 1 or 2;

B is –O-;

R_5, R_6, R_7, R_8 are independently hydrogen;

e = 0;

f = 0;

D and E are a chemical bond;

Z is $-CO_2H$;

R' is lower alkyl, halo, alkoxy, aryloxy or aralkyl; and

R" is lower alkyl or halo.

30. A compound according to claim 27 wherein

a = 0-2;

b = 0-1;

A is -O- or $-NR_{13}$-;

c+d = 1 or 2;

B is -O-;

R_1, R_2, R_3, R_4 R_5, R_6, R_7, and R_8 are independently hydrogen;

R_{13} is hydrogen, $R_{22}OC$-, or alkyl;

e = 0;

f = 0;

D and E are a chemical bond;

Z is $-CO_2H$;

R' is lower alkyl, halo, alkoxy, aryloxy or aralkyl; and

R" is lower alkyl or halo.

31. A compound according to claim 27 wherein

a = 1 or 2;

A is -O-;

b = 0;

R_1, R_2, R_7 and R_8 are independently hydrogen;

is optionally substituted phenyl;

c = 0;

B is -O-;

d = 1;

e = 0;

f = 0;

D and E are a chemical bond;

R' is hydrogen, halo or benzyloxy;

R" is lower alkyl, preferably methyl;

Z is $-CO_2H$.

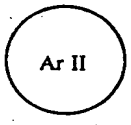
32. A compound according to claim 27 wherein:

a = 1 or 2;

A is -O-;

b = 0;

R_1, R_2, R_5 and R_6 are independently hydrogen;



is optionally substituted phenyl;

c = 1;

B is -O-;

d = 0;

e = 0;

f = 0;

D and E are a chemical bond;

R' is hydrogen, halo or benzyloxy;

R" is lower alkyl, preferably methyl;

Z is $-CO_2H$.

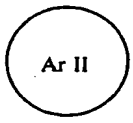
33. A compound according to claim 27 wherein:

a = 1 or 2;

A is -O-;

b = 0;

R_1, R_2, R_7, R_8, R_{11} and R_{12} are independently hydrogen;



is optionally substituted phenyl;

c = 0;

B is -O-;

d = 1;

e = 0;

f = 1;

D and E are a chemical bond;

R' is halo;

R" is lower alkyl, preferably methyl;

Z is $-CO_2H$.

34. A compound according to claim 27 wherein:

a = 1;

A is -O-;

b = 0;

c = 0-1;

B is -O-;

d = 0 or 1, wherein c+d = 1 or 2;

e = 0;

f = 0;

D and E are a chemical bond;

R' is hydrogen, aralkoxy, or halo;

R" is lower alkyl, preferably methyl;

Z is $-CO_2H$.

35. A compound according to claim 27 wherein:

a = 1;

A is -O-;

b = 0;

c = 0;

B is -O-;

d = 1;

e = 0;

f = 0;

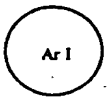
D and E are a chemical bond;

R' is hydrogen;

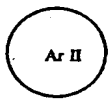
R" is lower alkyl;

Z is $-CO_2H$.

36. A compound according to claim 27 wherein:



and



are aryl or heteroaryl;

a = 1;

A is -O-;

b = 0;

c = 0;

B is -O-;

d = 1;

e = 0;

f = 0;

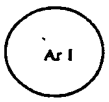
D and E are a chemical bond;

R' is hydrogen;

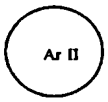
R" is lower alkyl;

Z is $-CO_2H$.

37. A compound according to claim 27 wherein:



is optionally substituted azaheteroaryl;



is optionally substituted phenyl;

a = 1;

A is -O-;

b = 0;

c = 0;

B is -O-;

d = 1;

e = 0;

f = 0;

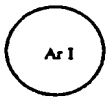
D and E are a chemical bond;

R' is hydrogen;

R" is lower alkyl;

Z is CO_2H.

38. A compound according to claim 27 wherein:



is optionally substituted quinolinyl, or a 5-membered heteroaryl group wherein the heteroaryl group is substituted by optionally substituted phenyl or optionally substituted cyclohexyl;

is optionally substituted phenyl;

a = 1;

A is –O-;

b = 0;

c = 0;

B is –O-;

d = 1;

e = 0;

f = 0;

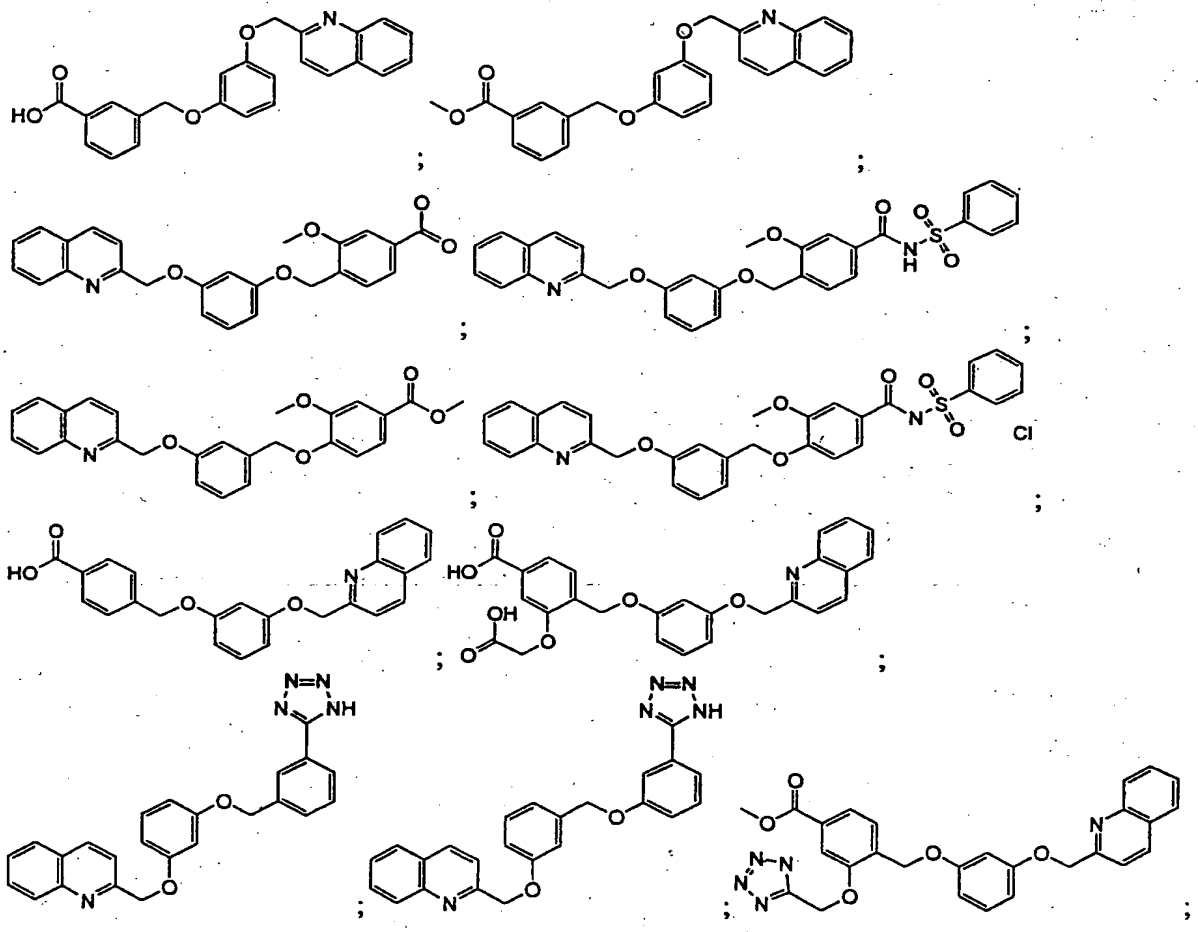
D and E are a chemical bond;

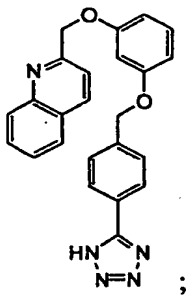
R' is hydrogen;

R" is lower alkyl;

Z is CO_2H.

39. A compound according to claim 1 selected from the group

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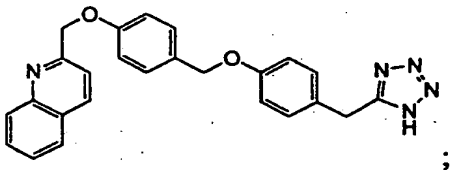
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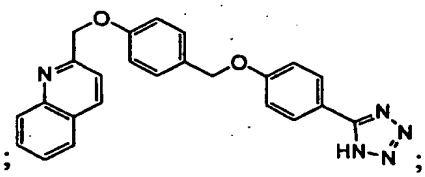
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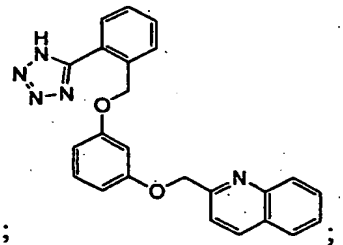
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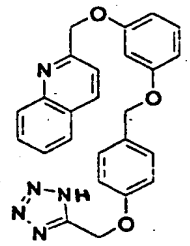
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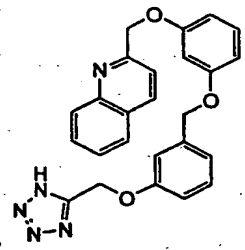
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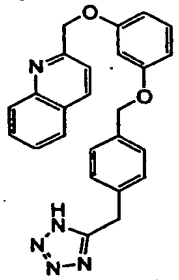
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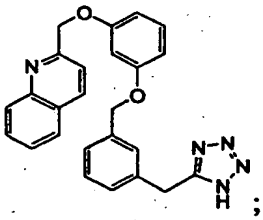
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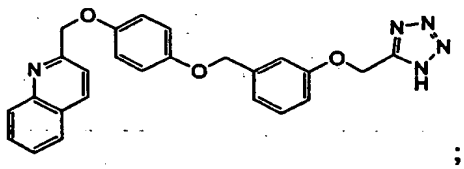
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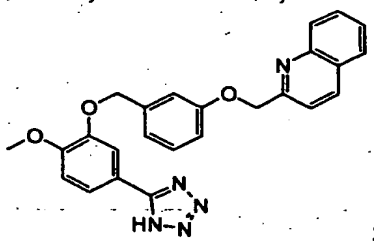
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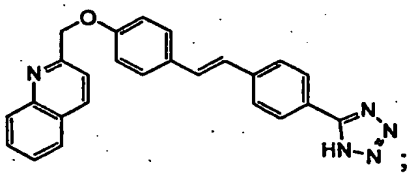
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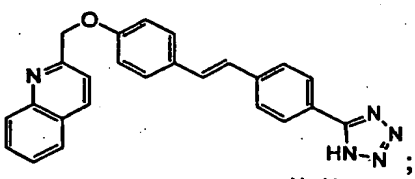
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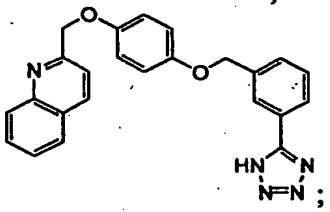
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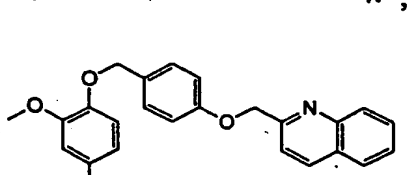
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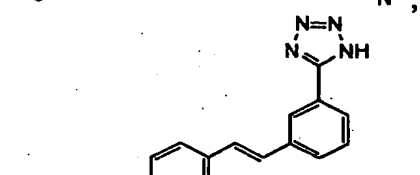
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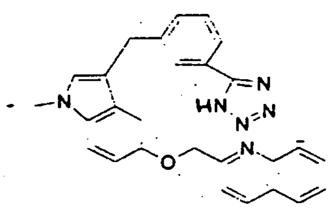
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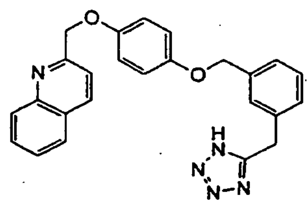
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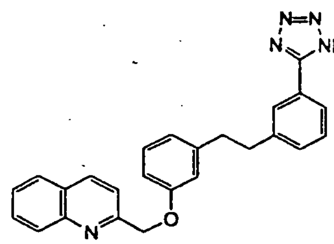
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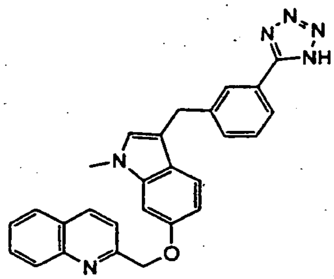
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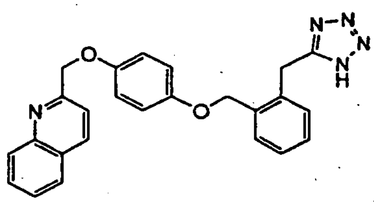
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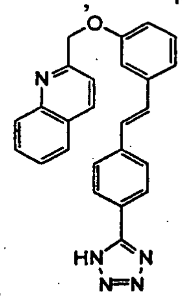
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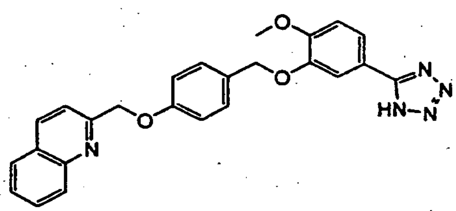
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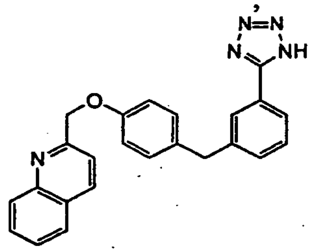
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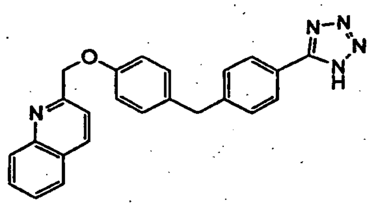
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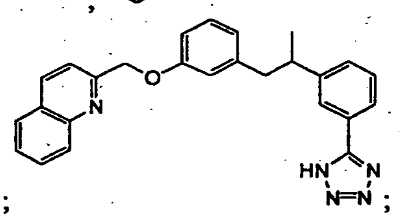
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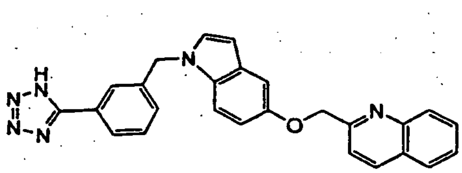
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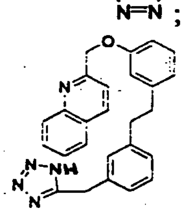
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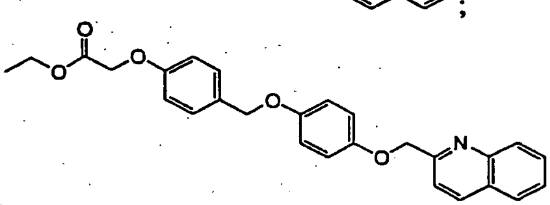
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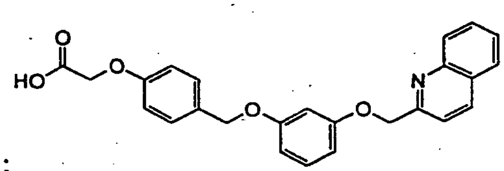
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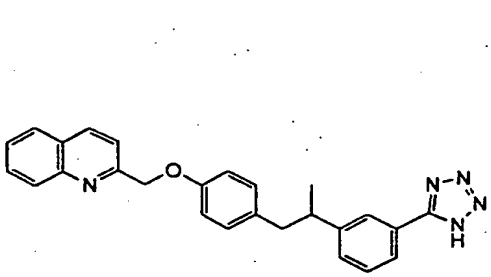
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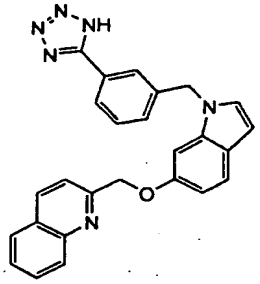
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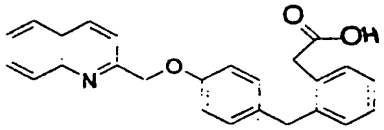
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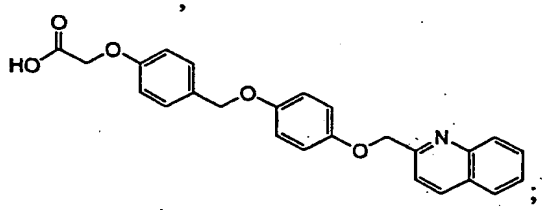
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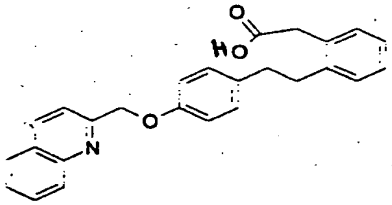
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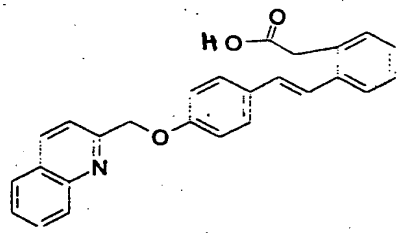
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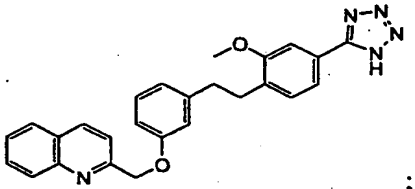
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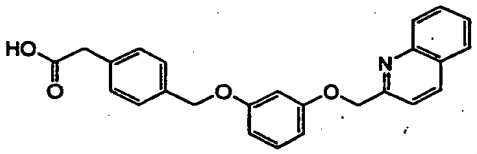
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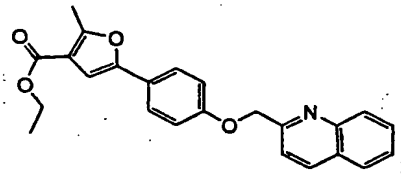
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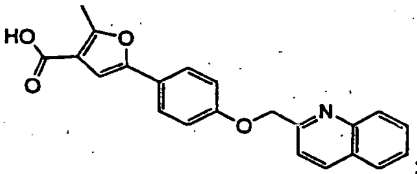
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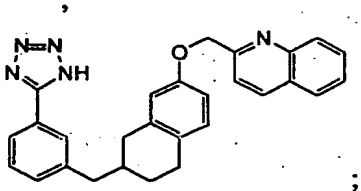
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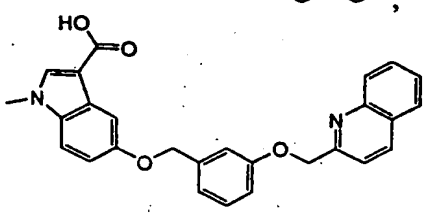
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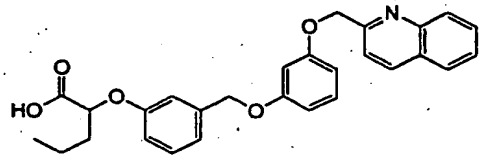
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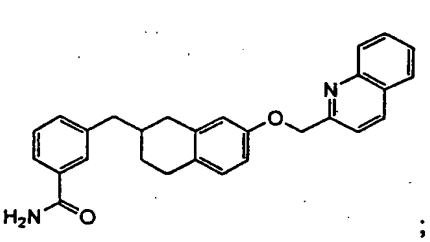
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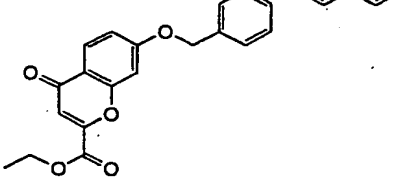
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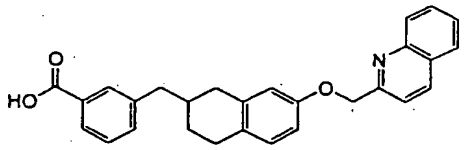
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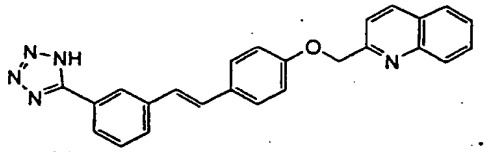
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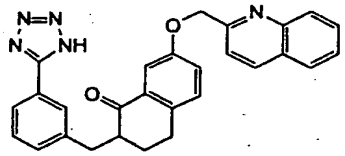
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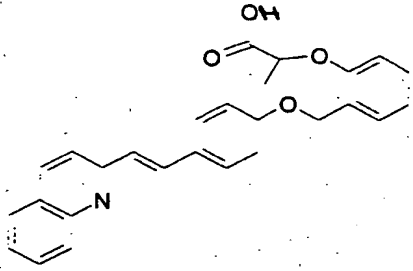
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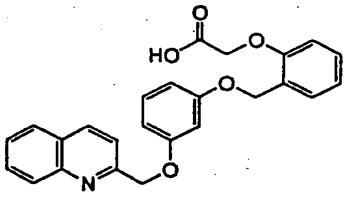
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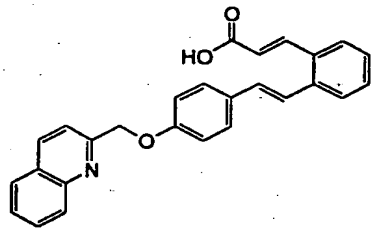
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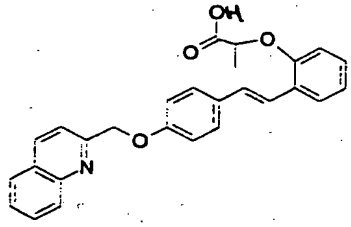
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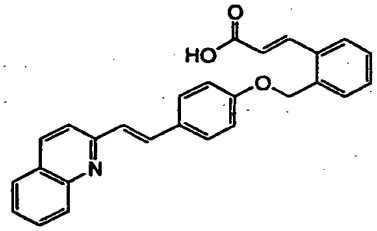
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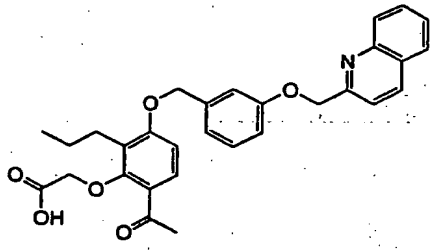
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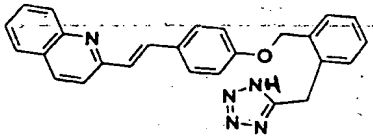
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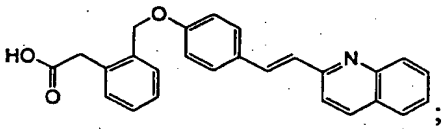
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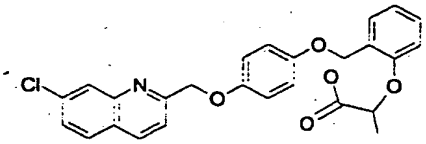
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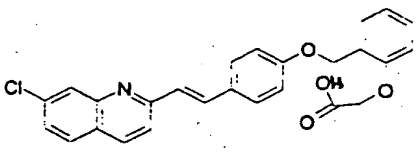
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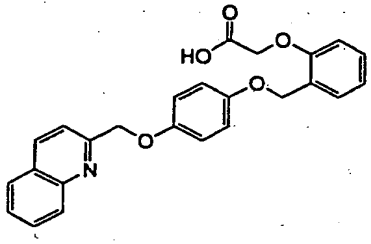
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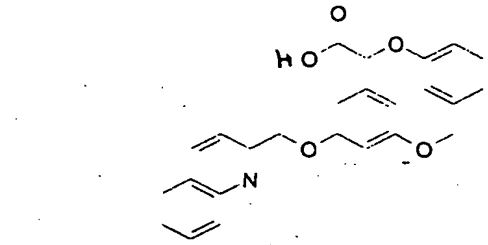
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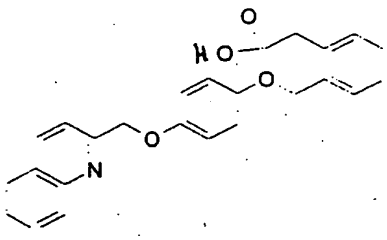
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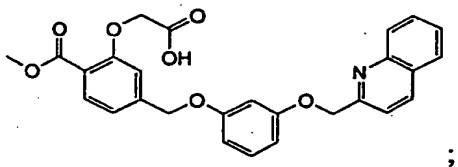
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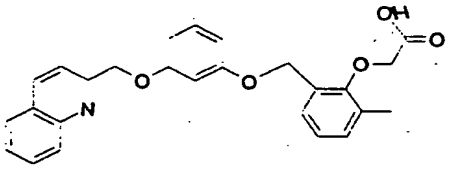
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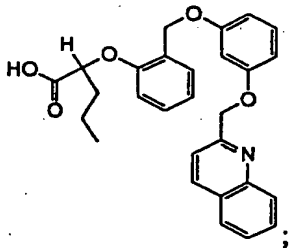
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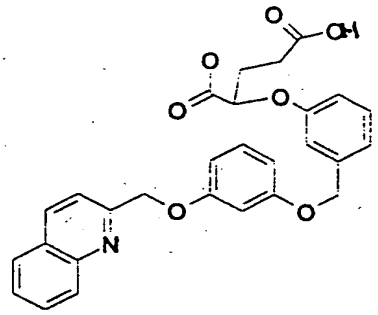
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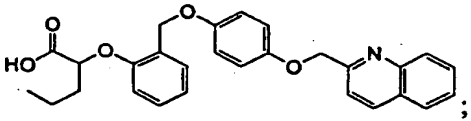
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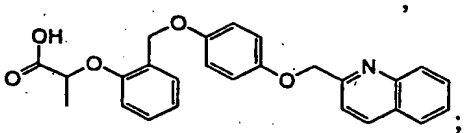
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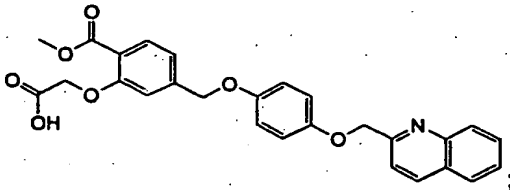
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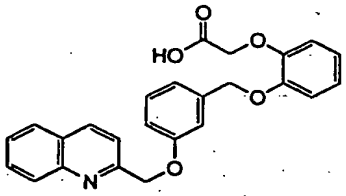
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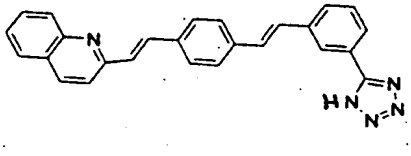
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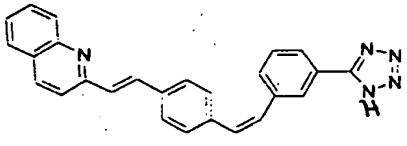
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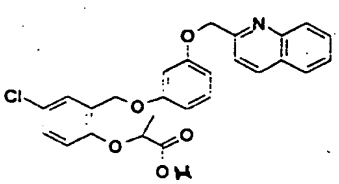
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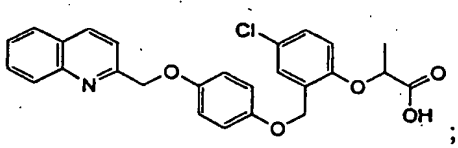
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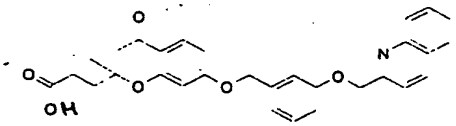

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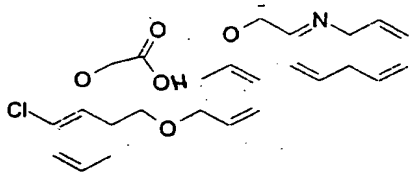

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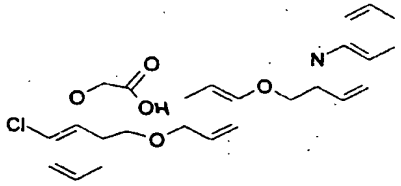

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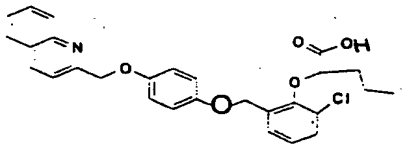

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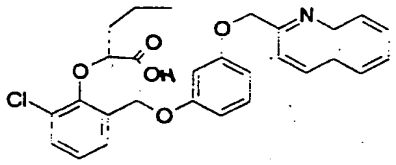

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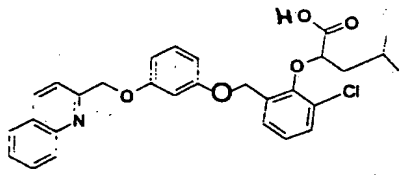

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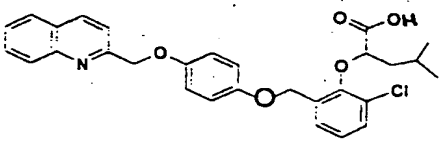

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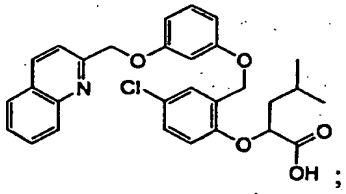

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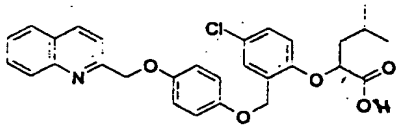

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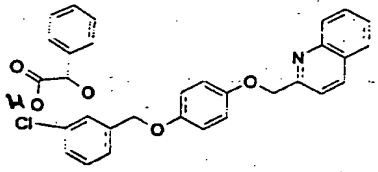

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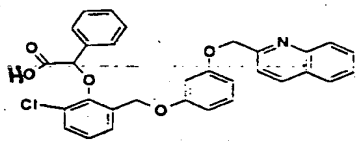

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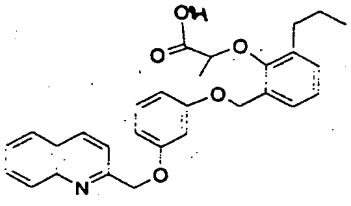

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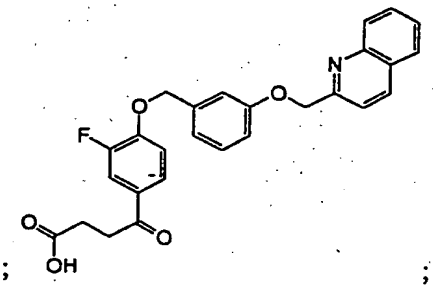

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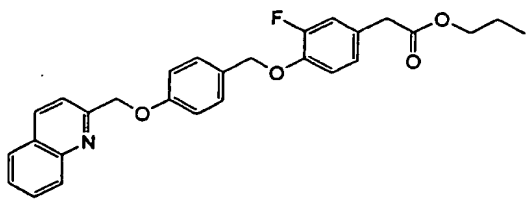
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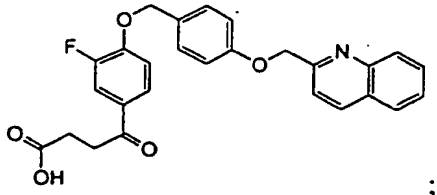
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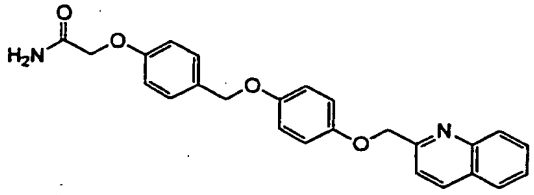
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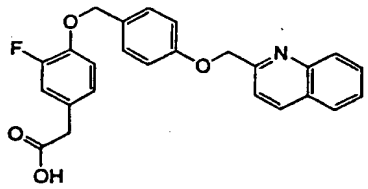
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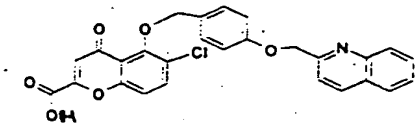
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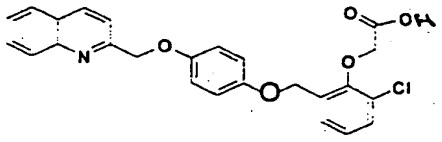
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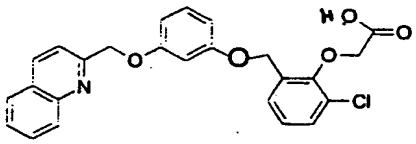
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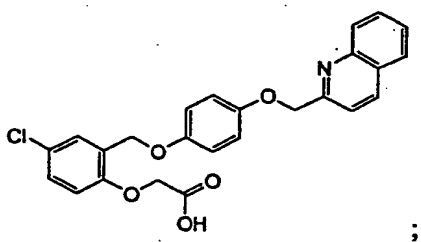
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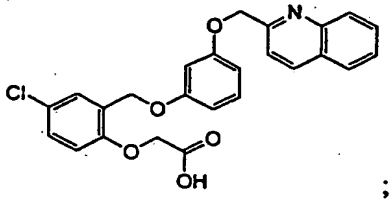
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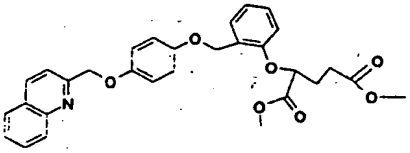
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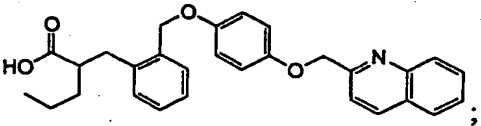
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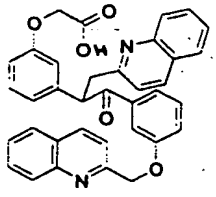
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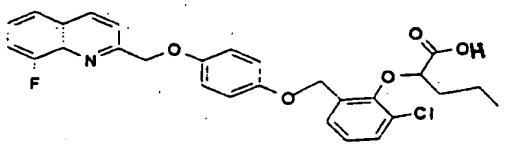
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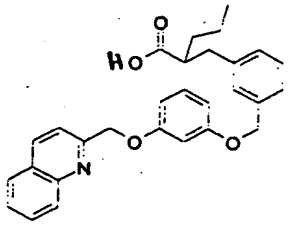
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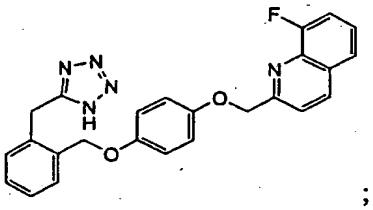
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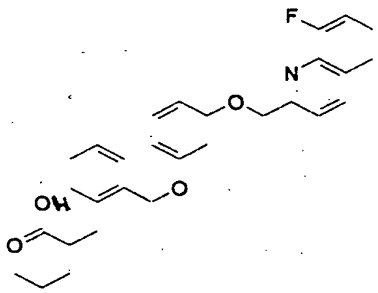
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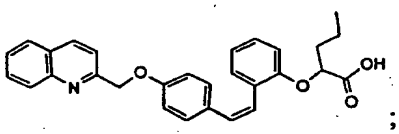
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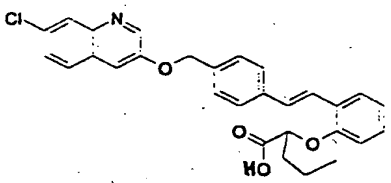
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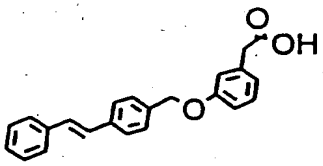
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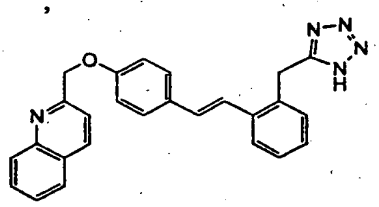
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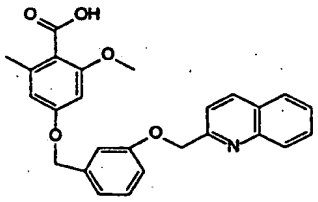
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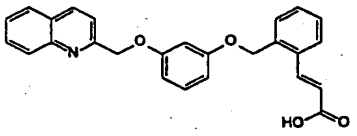
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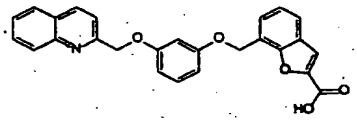
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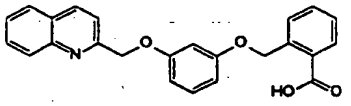
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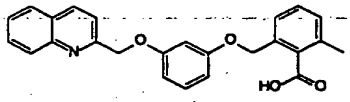
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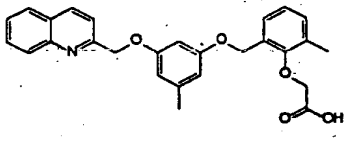
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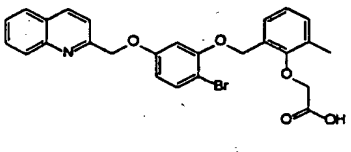
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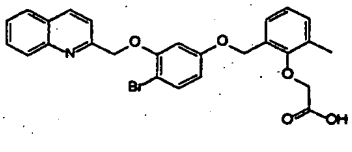
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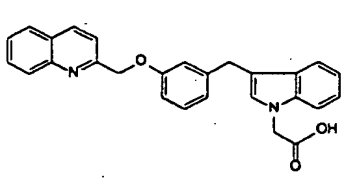

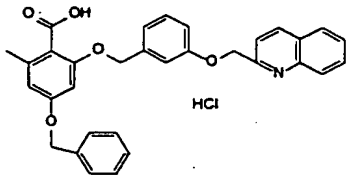

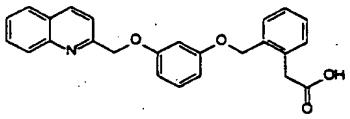

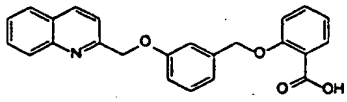

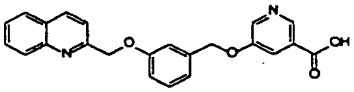

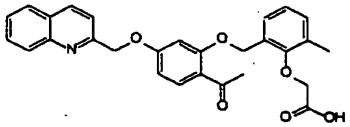

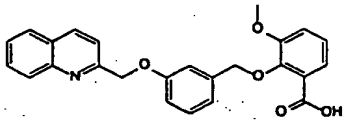

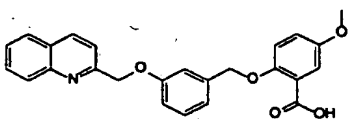

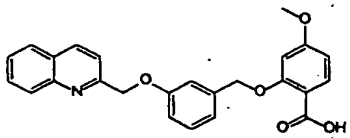

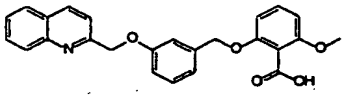

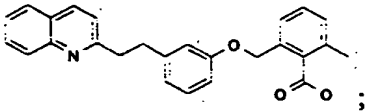

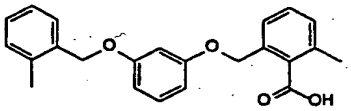

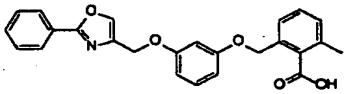

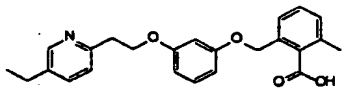

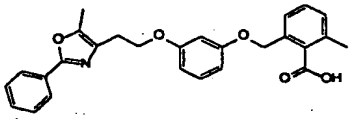

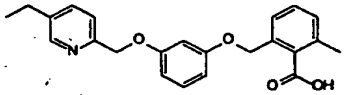

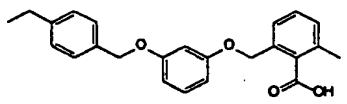

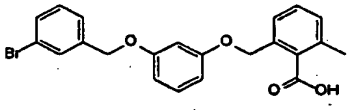

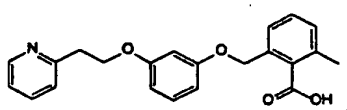

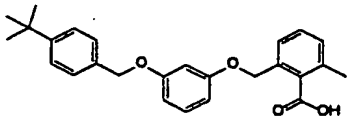

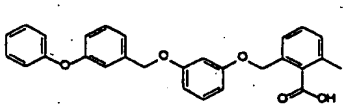

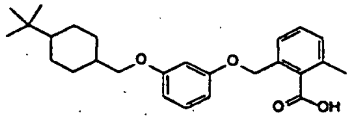

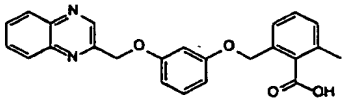

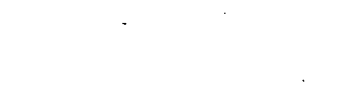

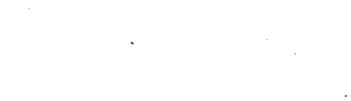

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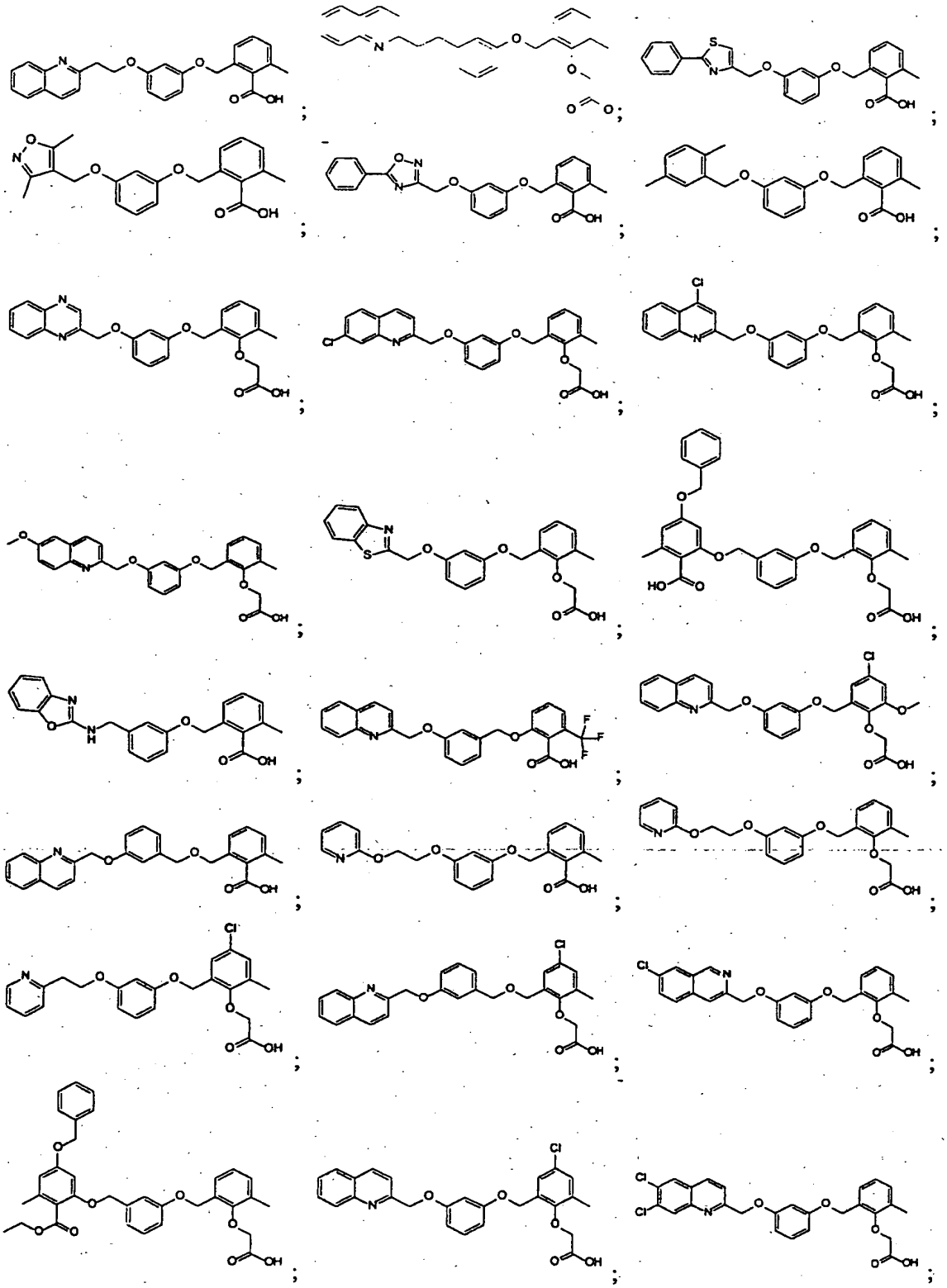

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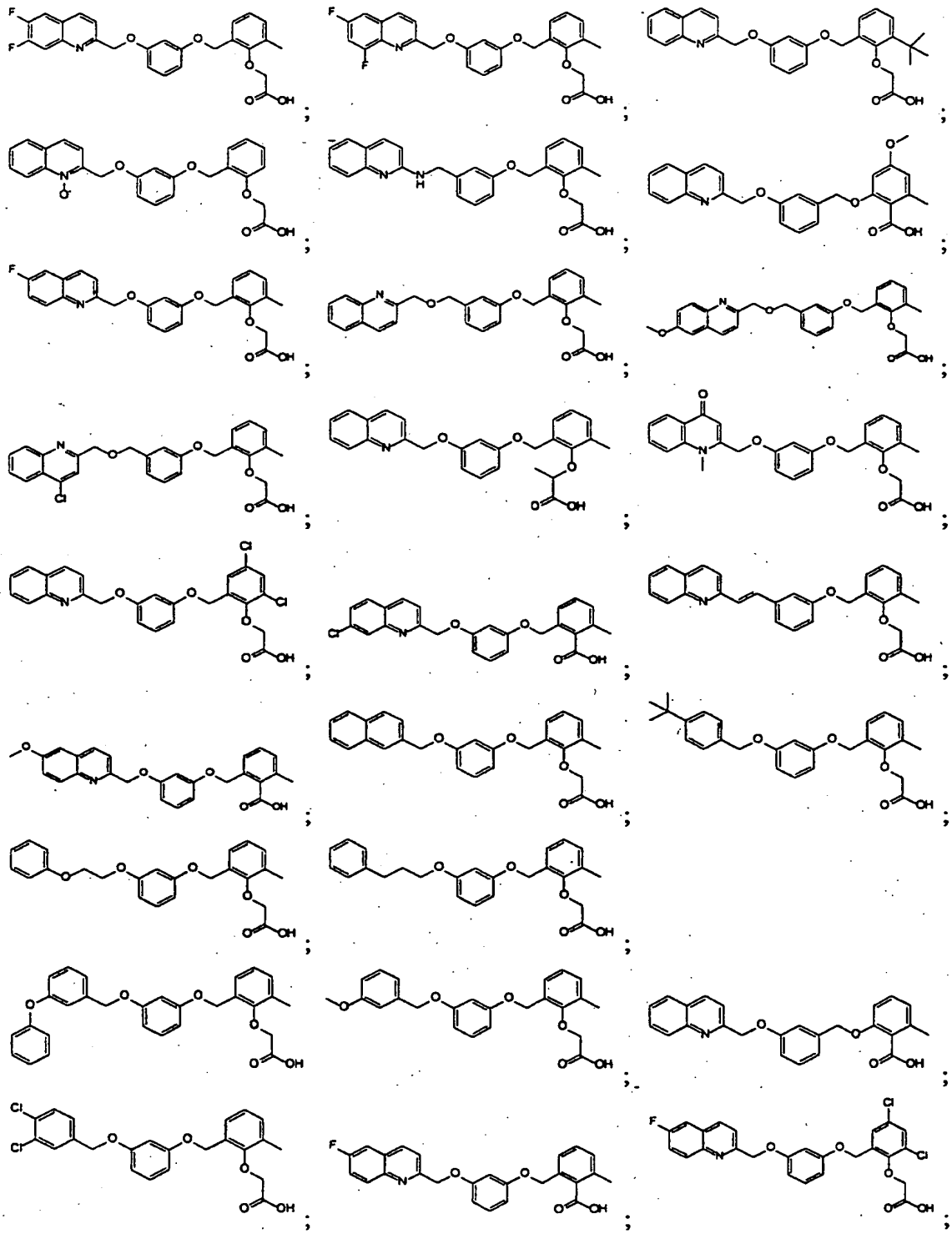
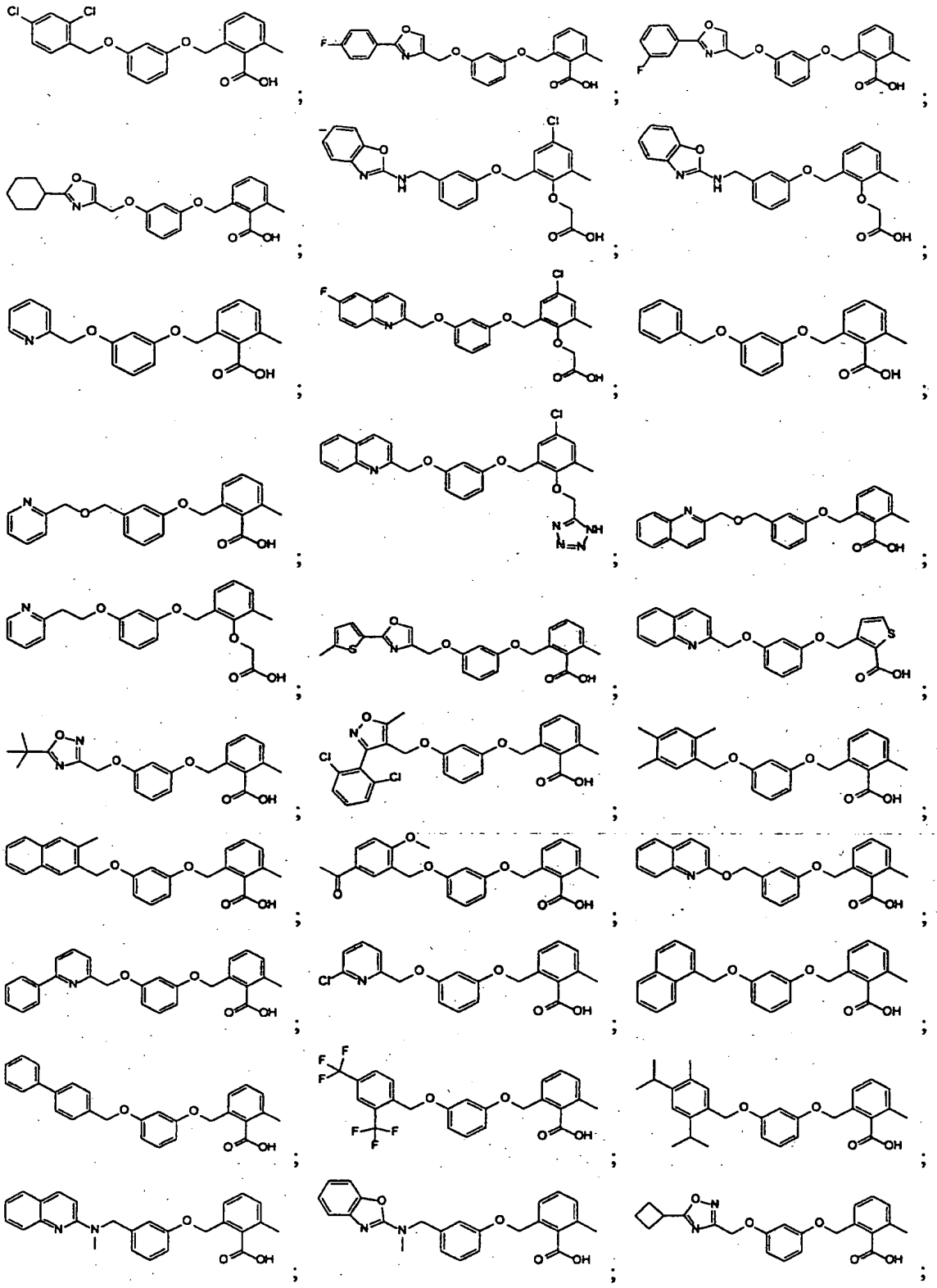
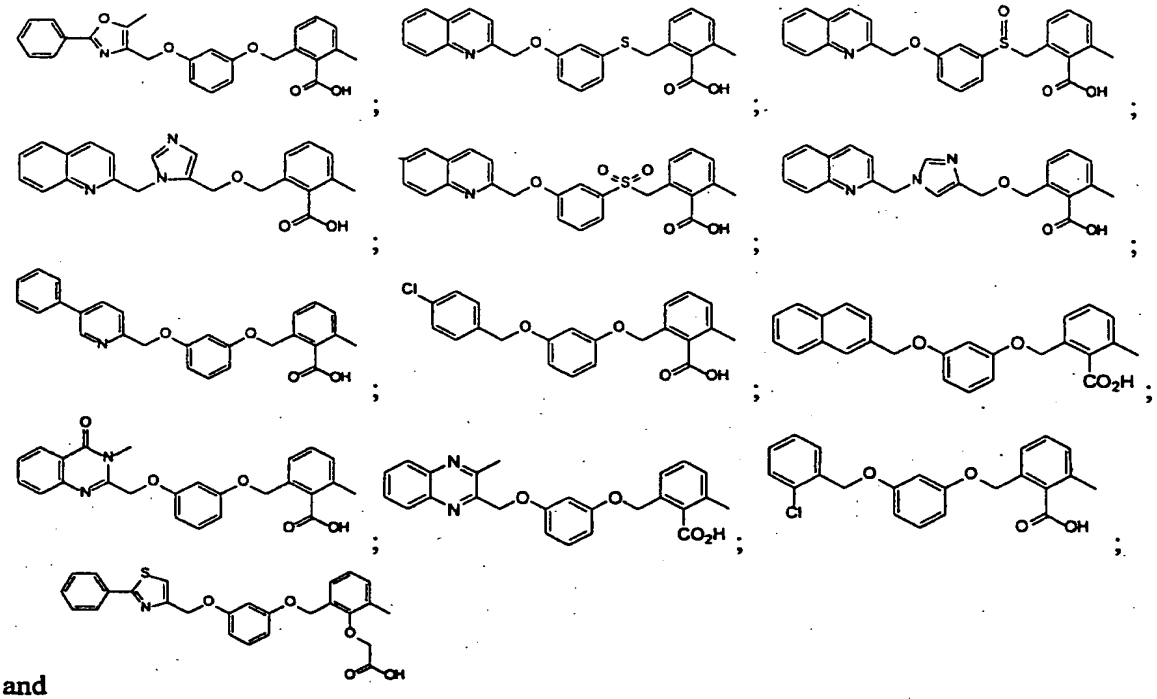
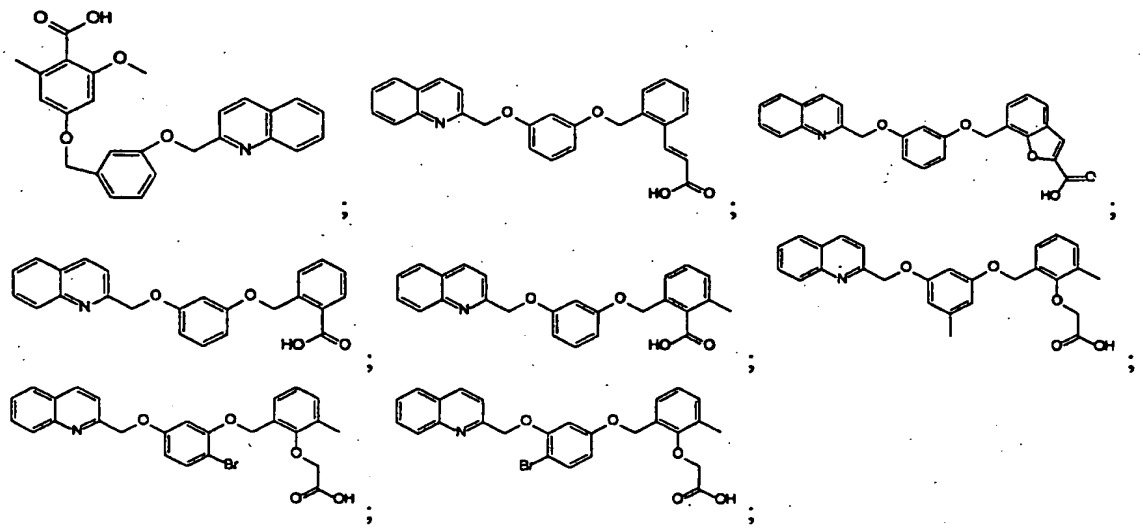


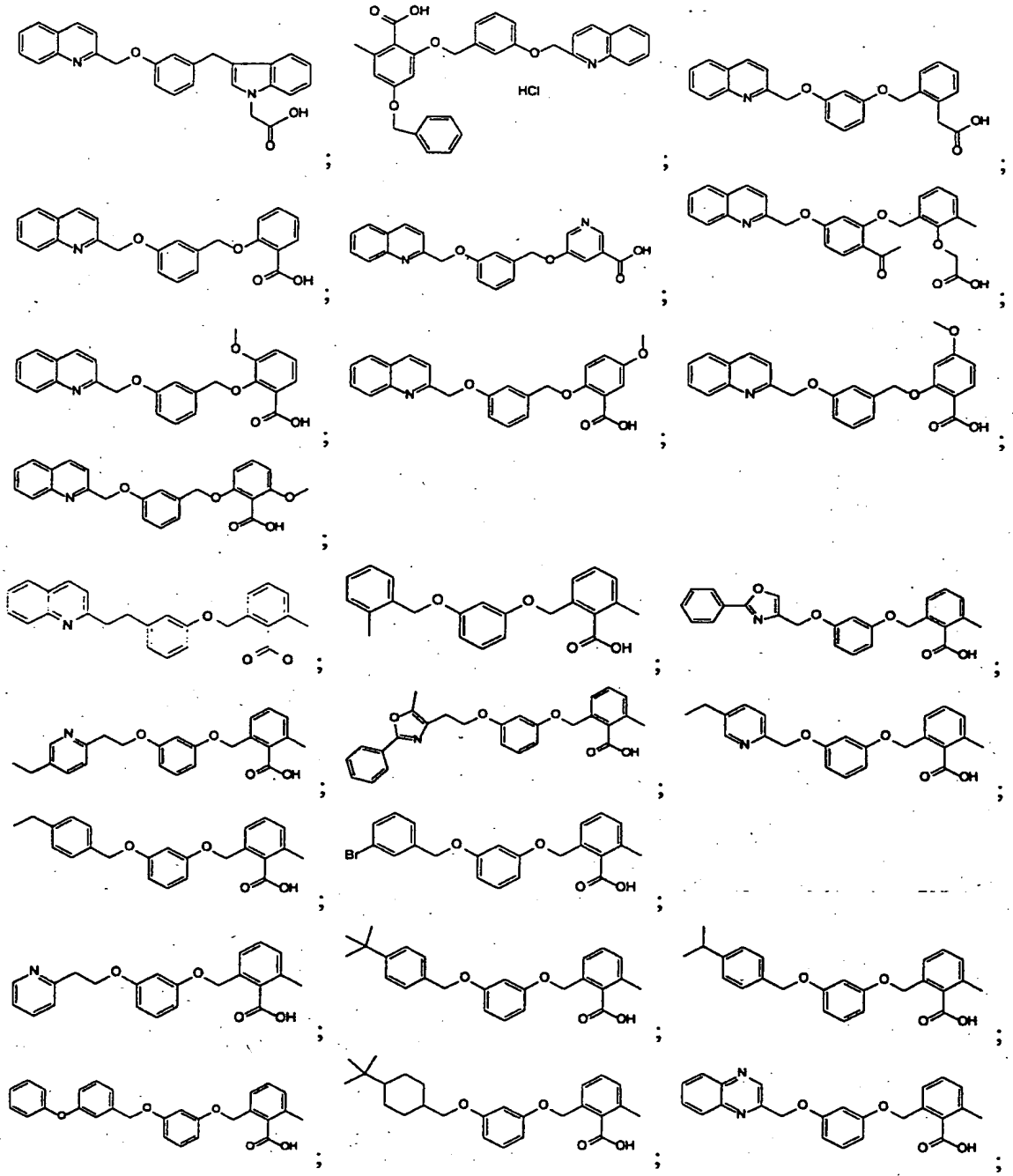


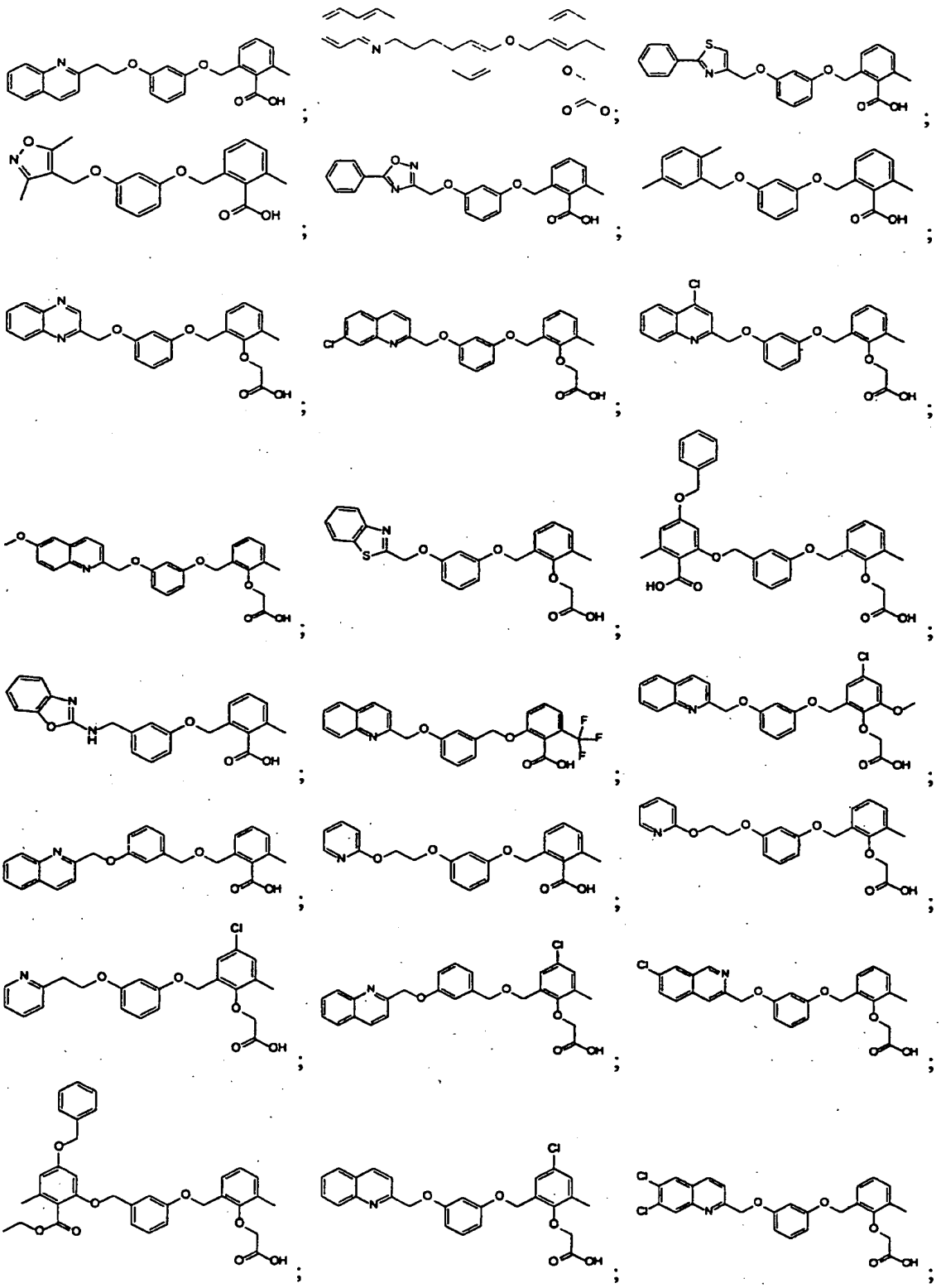


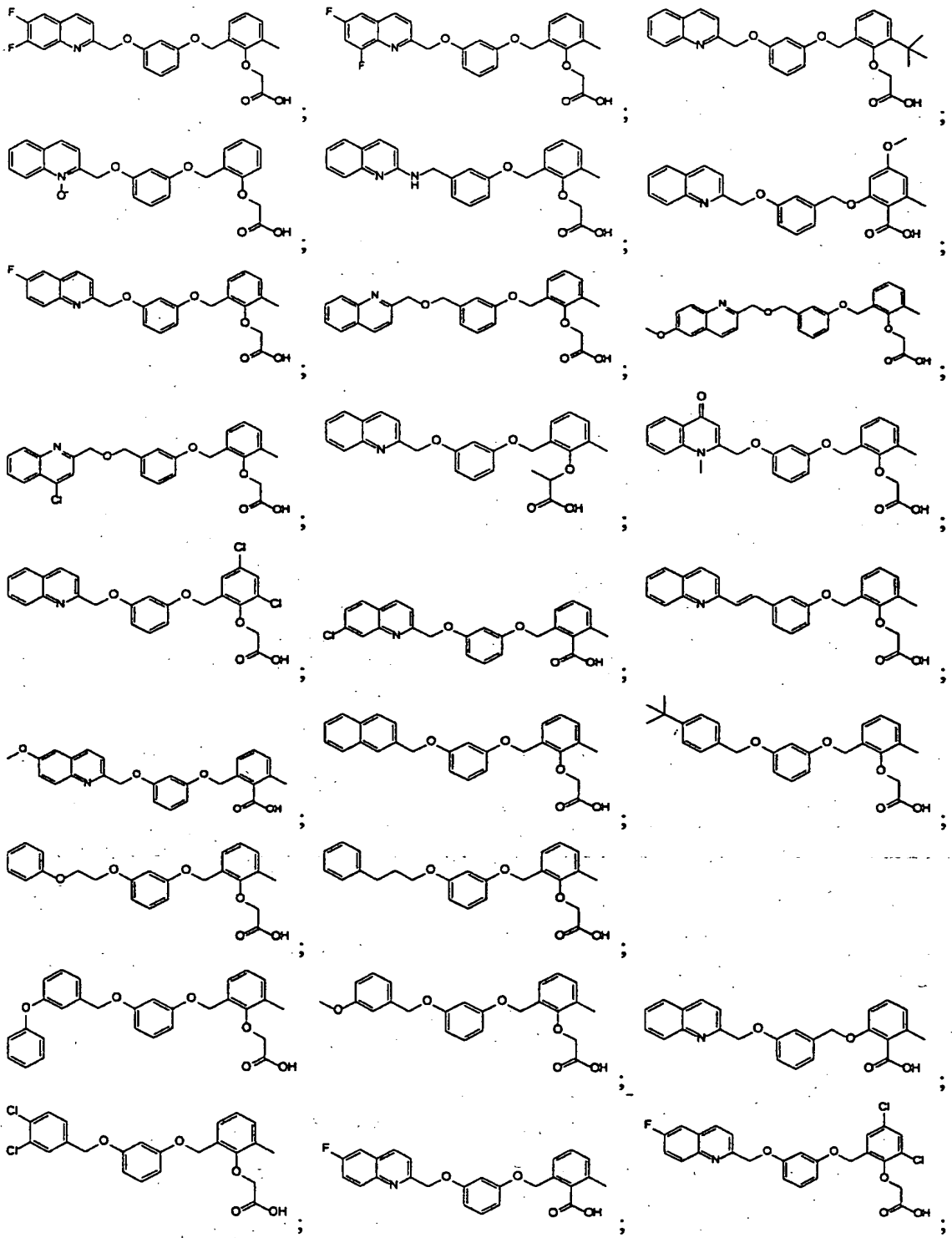
and

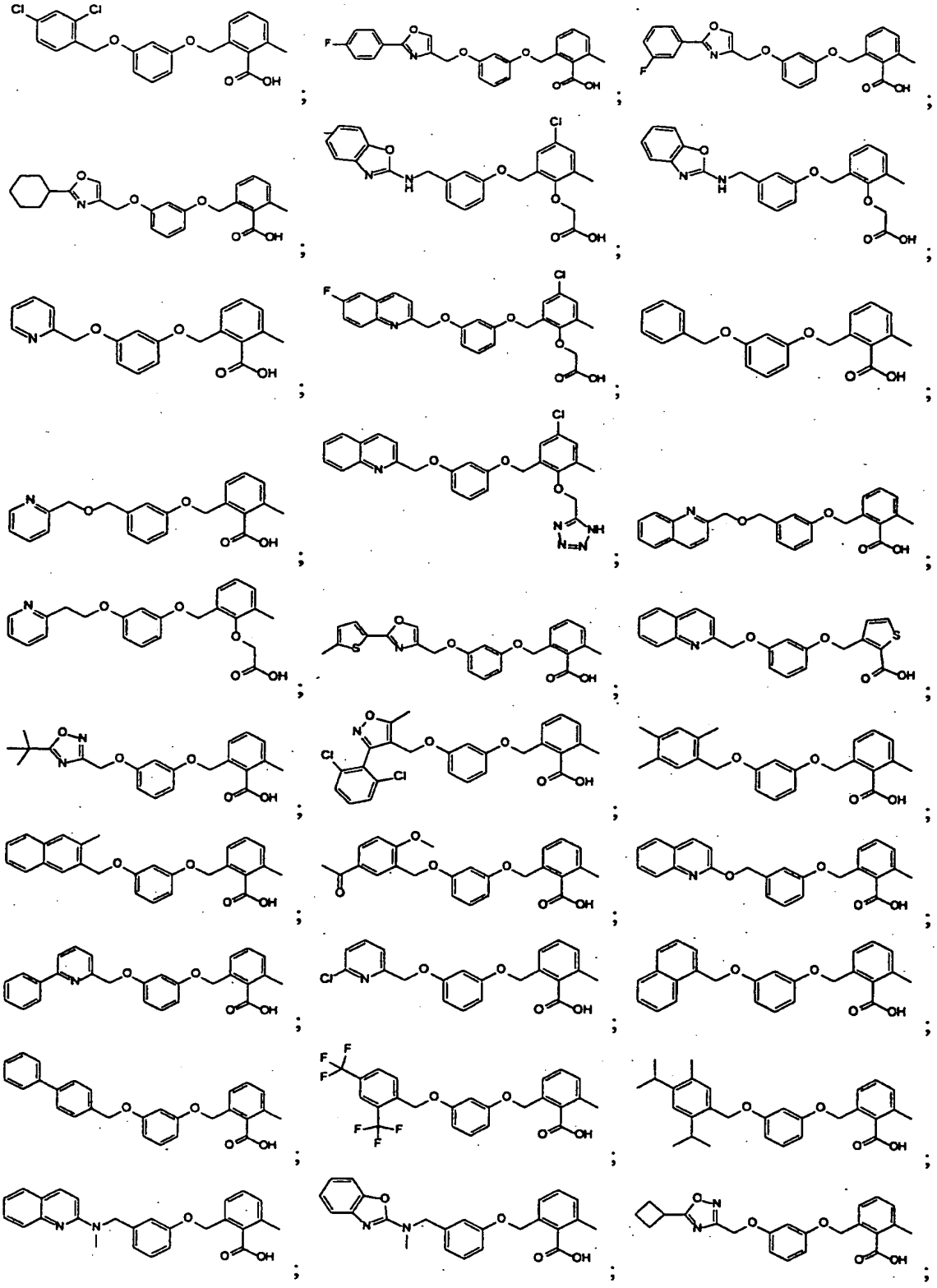
40. A compound according to claim 1 selected from the group consisting of

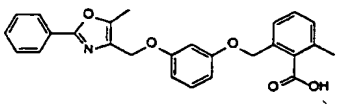








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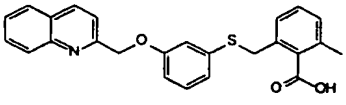
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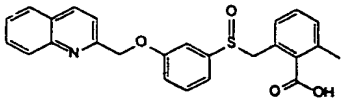
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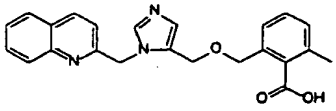
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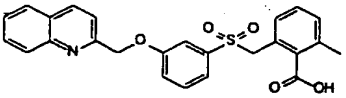
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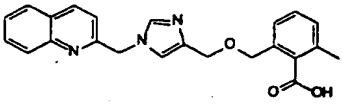
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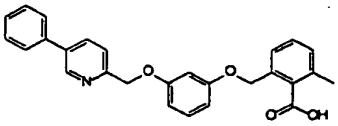
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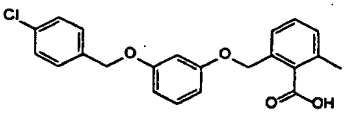
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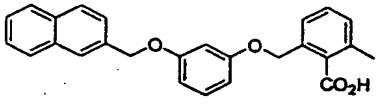
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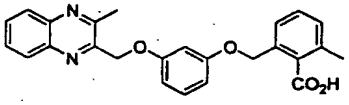
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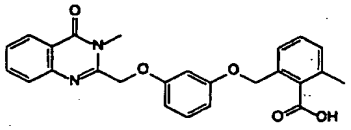
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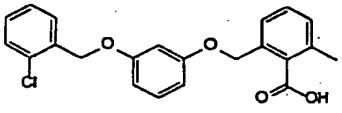
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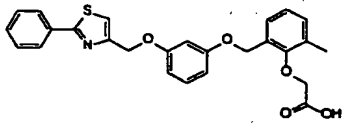
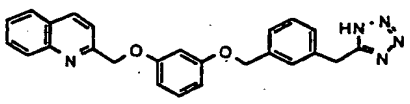


5 and

41. A compound according to claim 1 selected from the group consisting of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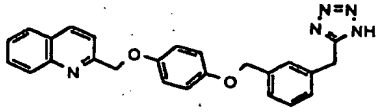
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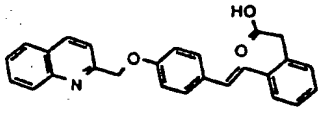
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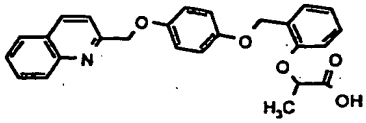
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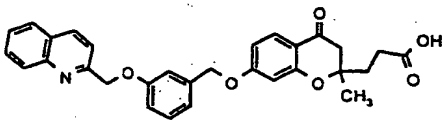
10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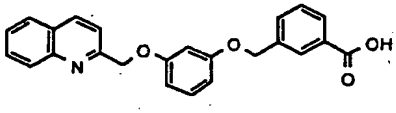
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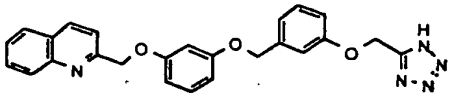
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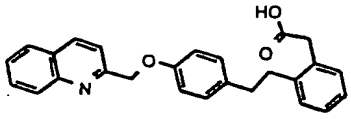
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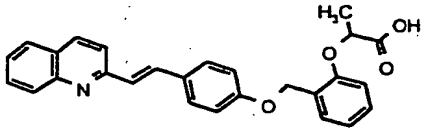
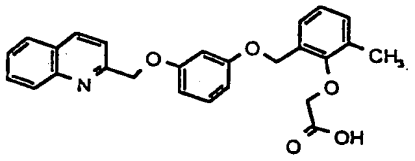
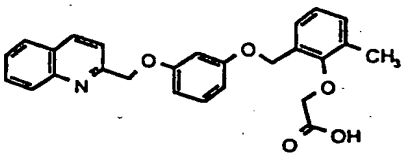


; and

42. A compound according to claim 1 selected from the group consisting of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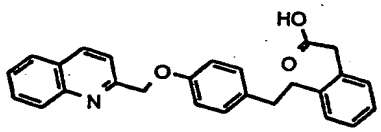
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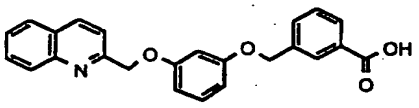
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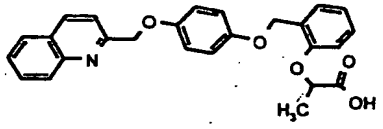
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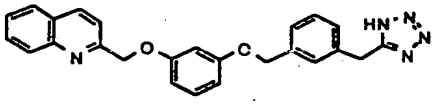
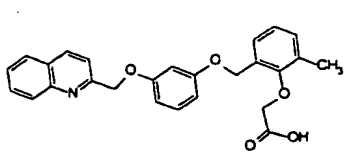

and

43. A compound according to claim 1 selected from the group consisting of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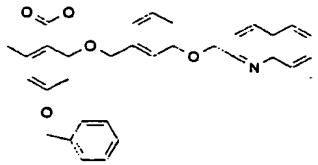
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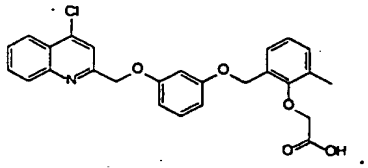
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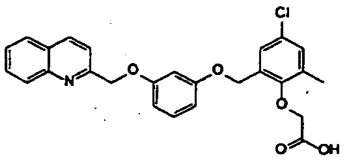
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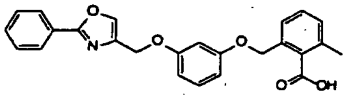
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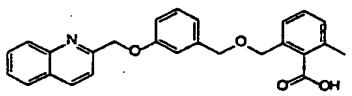
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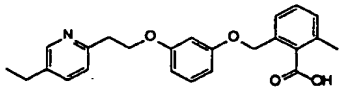
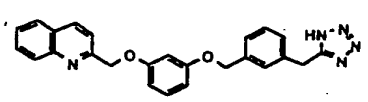
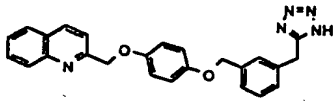
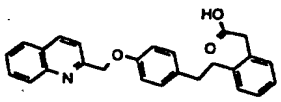

and .

44. A compound according to claim 1 selected from the group consisting of



; and

45. A compound according to claim 1 selected from the group consisting of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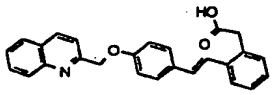
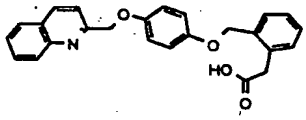
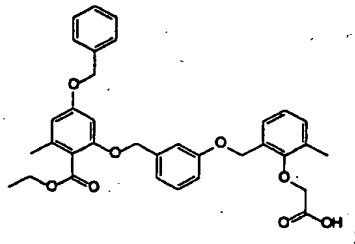

; and


46. A compound according to claim 1 selected from the group consisting of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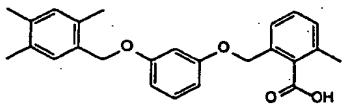
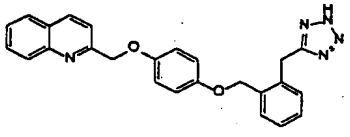
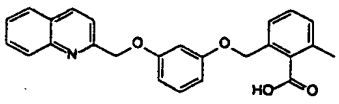
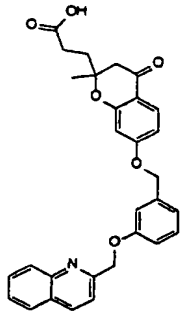

; and

.

47. A compound according to claim 1 selected from the group consisting of


.

48. A compound according to claim 1 of the formula



49. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

50. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound according to claim 1 having PPAR ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

51. A method according to claim 50 wherein the disease is associated with a physiological detrimental blood level of insulin, glucose, free fatty acids (FFA), or triclycerides.

52. The method according to claim 51, wherein the physiological disorder is hyperglycemia.

53. The method according to claim 52, wherein the hyperglycemia is diabetes

54. The method according to claim 52, wherein the hyperglycemia is Type II diabetes.

55. The method according to claim 51, wherein the physiological disorder is hyperinsulinism.

56. The method according to claim 55, wherein the hyperinsulinism is Syndrome X.

57. The method according to claim 51, wherein the physiological disorder is insulin resistance.

58. The method according to claim 51, wherein the physiological disorder is cardiovascular condition.

59. The method according to claim 58, wherein the cardiovascular condition is atherosclerosis.

60. The method according to claim 51, wherein the physiological disorder is hyperlipidemia.

61. The method according to claim 51, wherein the physiological disorder is hypertension.

62. The method according to claim 51, wherein the physiological disorder is an eating disorder.

63. The method according to claim 50 wherein the mediating is agonistic.

64. The method according to claim 50 wherein the mediating is antagonistic.

65. A method for mediating the activity of PPAR-γ receptor comprising contacting said PPAR-γ receptor with a compound of according to claim 1.

66. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 27 and a pharmaceutically acceptable carrier.

67. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound according to claim 27 having PPAR ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

68. A method according to claim 67 wherein the disease is associated with a physiological detrimental blood level of insulin, glucose, free fatty acids (FFA), or triclycerides.

69. The method according to claim 67, wherein the physiological disorder is hyperglycemia.

70. The method according to claim 69, wherein the hyperglycemia is diabetes

71. The method according to claim 69, wherein the hyperglycemia is Type II diabetes.

72. The method according to claim 67, wherein the physiological disorder is hyperinsulinism.

73. The method according to claim 72, wherein the hyperinsulinism is Syndrome X.

74. The method according to claim 67, wherein the physiological disorder is insulin resistance.

75. The method according to claim 67, wherein the physiological disorder is cardiovascular disorder.

76. The method according to claim 75, wherein the cardiovascular disorder is atherosclerosis.

77. The method according to claim 67, wherein the physiological disorder is hyperlipidemia.

78. The method according to claim 67, wherein the physiological disorder is hypertension.

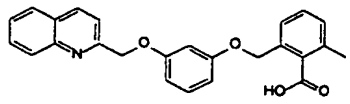
79. The method according to claim 67, wherein the physiological disorder is an eating disorder.

80. The method according to claim 67 wherein the mediating is agonistic.

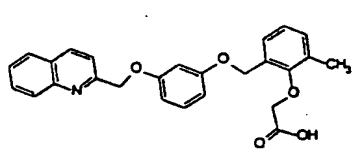
81. The method according to claim 67 wherein the mediating is antagonistic.

82. A method for mediating the activity of PPAR receptor comprising contacting said PPAR receptor with a compound of according to claim 27.

83. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound having PPARα and PPARγ ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, wherein said compound is of the formula



84. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound having PPARα ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of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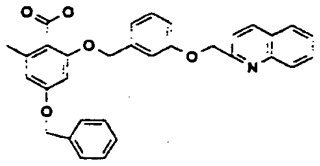
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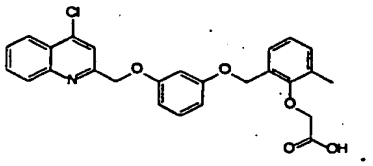
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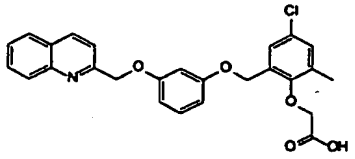
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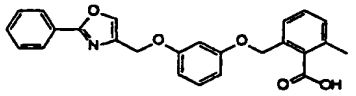
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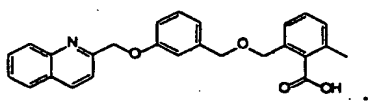
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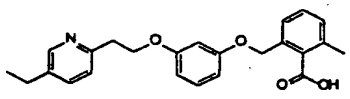
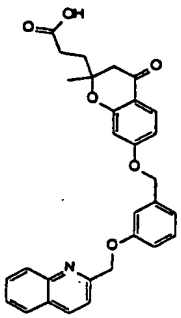
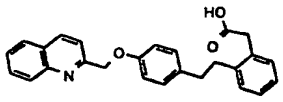
and


85. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound having PPARδ ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, wherein said compound is of the formula:



86. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound having PPARα and PPARδ ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a

pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of: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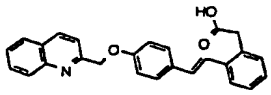
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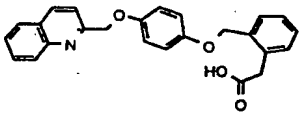
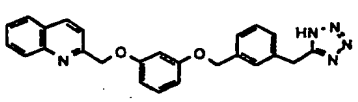
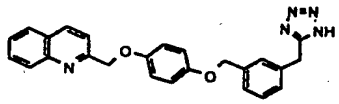
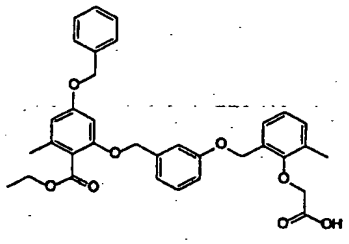


87. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound having PPARδ and PPARγ ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:



; and

88. A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound having PPARγ ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of: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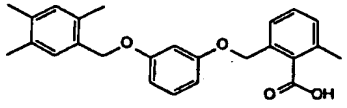
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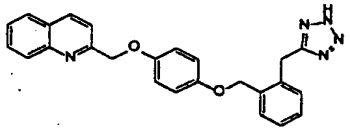

INTERNATIONAL SEARCH REPORT

Internation. pplication No
PCT/US 00/11490

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/14 A61K31/33 A61K31/19 A61P43/00 C07D401/12
C07D401/14 C07D215/18 C07D405/12 C07D263/32 C07D213/30
C07D241/42 C07D277/24 C07D261/08 C07D271/06 C07D277/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 27857 A (MERCK & CO., INC.) 7 August 1997 (1997-08-07) * complete document *	1,49,66, 82
X	WO 98 27974 A (MERCK & CO., INC.) 2 July 1998 (1998-07-02) * complete document *	1,49,66, 82
X	WO 97 31907 A (GLAXO GROUP LTD.) 4 September 1997 (1997-09-04) * complete document *	1,49,66, 82
X	WO 97 28149 A (MERCK & CO., INC.) 7 August 1997 (1997-08-07) * complete document *	1,49,66, 82

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2000	04/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Bijlen, H

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Internatior. pplication No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/58 C07D215/38 C07D215/20 C07D413/04 C07D409/12
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C07C57/03

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 24331 A (LABORATORIOS MENARINI S.A.) 10 July 1997 (1997-07-10) * complete document * ---	1,49
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Bijlen, H

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INTERNATIONAL SEARCH REPORT

International application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-88 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).
For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentioned claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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Internatio. Application No
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